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[54] **CONTRACEPTIVE METHOD AND COMPOSITION**

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[63] Continuation of Ser. No. 721,614, Apr. 16, 1968, Abandoned.

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.** **A61k 17/00**

[58] **Field of Search** 424/243

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[57] **ABSTRACT**

Conception is prevented in a female of reproductive age without suppressing ovulation by administering to such female within the period starting with the fifth and ending with the eighth day of the menstrual cycle an effective amount of a progestogene which when administered in such amount effective for preventing conception has at most an insignificant suspension effect on gonadotropin secretion.

1 Claim, No Drawings

CONTRACEPTIVE METHOD AND COMPOSITION

This application is a continuation of Ser. No. 721,614 filed Apr. 16, 1968, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to a contraceptive method and composition and, more particularly, the present invention is concerned with the administration of a contraceptive agent which, upon a single administration, will prevent conception for a prolonged period of time, such as one menstrual cycle or longer without inhibiting ovulation.

Several methods for preventing conception have been proposed which require, for instance, oral administration of combinations of estrogenic and progestogenic agents, commercially available, for instance under the tradenames Enovid, Ovulen and Anovlar.

It has also been proposed to prevent conception by parenteral administration of corresponding preparations which, additionally, possess a prolonged effect. Thus, for instance, in an article published in "Obstetrics and Gynecology", Volume 21, No. 6, June 1963, Irving Siegel proposed to use, as ovulation inhibitors for women, hydroxy-progesterone caproate in monthly doses of 500 mg. each. Such injections resulted in entirely inhibiting ovulation. Similarly, in an article published in "Fertility and Sterility", Volume 17, March-April 1966, E. M. Coutinho et al describes also the administration of hydroxyprogesterone caproate as ovulation inhibitors for women. The tests carried out by Coutinho et al, included dosage ranges from 50 to 400 mg per injection, repeated at intervals of 1 to 3 months. Also these injections resulted in entire inhibition of ovulation.

These prior art methods are effective by causing suppression of ovulation. Thus, the contraceptive effect achieved thereby is based on a passivation of the ovaries, and the withdrawal bleeding which is induced by these methods cannot be compared with regular menstruation. In addition to several undesirable side effects which sometimes occur, such as stomach complaints, nausea, weight gain, and others, it is well known to those skilled in the art that these prior-art methods constitute a very severe interference with the normal endocrinological condition of the thus treated female.

It is therefore an object of the present invention to provide a safe, reliable and effective contraceptive method and a composition therefor, which are not subject to the above-discussed difficulties and disadvantages encountered in connection with the conventional administration of estrogenic and progestogenic combinations.

SUMMARY OF THE INVENTION

According to the present invention, conception is prevented without suppression of ovulation by parenterally administering to a female of reproductive age an effective amount of a progestogene selected from the group of progestogenes which when administered in such effective amount have at most an insignificant suspension effect on gonatropin secretion.

The progestogene may be administered intramuscularly or subcutaneously, or by implantation and preferably should be administered between the fifth and eighth day, both inclusive, of the menstrual cycle and in such amount that one administration will suffice at least for one cycle.

Preferably, the progestogene is administered in the form of an oily solution which also may include diluents and solubilizing agents.

The progestogenes which are administered according to the present invention preferably will be such which do not have a significant ovulation-suppressing and pituitary hypothalamic-inhibiting effect, or the ovulation-suppressing and pituitary hypothalamic-inhibiting effect of the administered progestogenes should be sufficiently small so that the threshold value of these effects is not reached when administering an amount thereof which is effective with respect to achieving the desired contraceptive result, i.e., which is sufficient to inhibit the periovulatory changes of the cervical mucus and endometrium which, it is thought, are substantially responsible for the desired contraceptive effect.

The present invention is also concerned with a composition in dosage form for parenteral administration for the purpose of achieving a contraceptive effect in a female of reproductive age, which composition comprises an effective amount of a progestogene of the type described above and a pharmaceutical diluent.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has now been found, and is proposed according to the present invention, to obtain a reliable contraceptive effect without simultaneous suppression of ovulation by the soe parenteral administration of a progestogene, whereby the contraceptive effect of one administration may last for one menstrual cycle or longer and the length of time for which conception is reliably prevented may be varied by utilizing progestogenes with more or less long-lasting effect and/or changing the dosage which is administered.

Thus, the method for preventing conception without suppression of ovulation, as proposed according to the present invention, provides parenteral, preferably intramuscular or subcutaneous, administration or implantation of a suitable progestogene.

It is achieved thereby that conception and nidation which is made possible by certain periovulatory changes, i.e. changes of the cervical mucus, the endometrium and probably also of the tubal motility, will be prevented according to the present invention by suppressing the periovulatory changes required for conception and nidation.

In order to be reliably effective, in accordance with the present invention, the administration of the progestogene preferably should be carried out about one day prior to the start of the above-described periovulatory changes. It is known that the periovulatory changes start about the eighth or ninth day after the beginning of the menstrual bleeding or the menstrual cycle. However, there are certain individual differences with respect to the exact time lapse between the start of the menstrual cycle and the start of the periovulatory changes and it is difficult to determine in the individual case the exact time of the periovulatory changes.

Consequently, it is suggested that the administration of the progestogene in accordance with the present invention should be carried out between the fifth and eighth day after the start of the menstrual cycle (both days inclusive) in order to achieve with certainty the desired contraceptive effect. A single administration of an effective amount of the progestogene will suffice for one menstrual cycle.

If it is desired to prevent conception for a period encompassing several menstrual cycles, the required dosage may be administered between the fifth and eighth day of each menstrual cycle.

In theory at least, it would be possible to administer the progestogene during the second and further-following cycles during other stages of the respective cycles; however, it would then be necessary to know for how long the progestogene administered in the preceding cycle will remain effective in order to assure also in the next-following cycle a reliable contraceptive effect.

It would be possible, if the effectiveness of the preceding administration has not extended to the time of the next administration, that the next administration may be carried out after periovulatory changes already have taken place. For this reason, if it is desired to administer the progestogene once during each cycle, it is preferred and suggested to have each administration within the fifth and eighth day after the start of the respective cycle. It may be possible by increasing the dosage to reverse already started periovulatory changes; however, it appears simpler and more desirable to require administration of the progestogene during each menstrual cycle between the fifth and eighth day thereof—if conception is to be prevented for one cycle.

By correspondingly increasing the amount of progestogene and particularly utilizing progestogenes having a long-lasting effect, it is also possible with a single administration of the progestogene to effectively prevent conception for two or even more menstrual cycles.

Progestogenes which may be used in accordance with the present invention include all progestogenes which, upon parenteral administration or implantation, will not have an ovulation-suppressing effect. Furthermore, the dosage of the progestogene should be so chosen that no suspension effect on gonadotropin secretion, or only an insignificant suspension effect, is caused thereby.

Preferred are the progestogenes which in addition to their progestogenic effect do not also cause pituitary hypothalamic inhibition, particularly do not have an ovulation-suppressing effect. As examples of progestogenes which give excellent results in accordance with the present invention, the esters of hydroxyprogesterone and of 19-nor-hydroxyprogesterone, particularly the corresponding 17-caproates and 17-oenenthates, may be mentioned.

A second group of suitable progestogenes includes those in which the desired progestogenic effect and the anti-estrogenic effect) is substantially dissociated from the undesirable ovulation-suppressing effect. For use of this type of progestogenes in accordance with the present invention, the dosage must be sufficiently small so that, on the one hand, the change in the composition and condition of the cervical mucus which is achieved thereby is sufficient for achieving a reliable contraceptive effect and, on the other hand, the threshold dosage of the pituitary hypothalamic inhibition will not be exceeded.

This group of suitable progestogenes includes progesterone and its pharmaceutically valuable 3-enol esters and pharmaceutically acceptable 17α-hydroxyprogesterone derivatives.

Specific compounds included in this group are the 17-esters with pharmaceutically acceptable acids of 6-α-methyl-17α-hydroxyprogesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxyprogesterone, 6-fluoro-6-dehydro-17α-hydroxyprogesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxyprogesterone-6-fluoro-6-dehydro-16α-methyl-17α-hydroxyprogesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxyprogesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxyprogesterone, 6,16-dimethyl-6-dehydro-17α-hydroxyprogesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxyprogesterone, 6-chloro-6-dehydro-16-methylene-17α-hydroxyprogesterone, 1,2-methylene-6-chloro-6-dehydro-17α-hydroxyprogesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxyprogesterone, and also 17α-ethinyl-18-homo-19-nortestosterone and esters thereof with pharmaceutically acceptable acids.

Basically, it is also possible to utilize for the purpose of the present invention progestogenes which have only relatively small dissociation between the desired progestogenic effect and the undesired ovulation-suppressing effect, such as nor-ethisterone caproate, 17α-ethinyl-testosterone, 17α-ethinyl-19-nortestosterone, 17α-ethinyl-$\Delta^{5(10)}$-oestrene-17β-ol-3-on, 17α-methyl-19-nor-testosterone, 17α-ethinyl-Δ^{4}-oestrene-3,17β-diol, 17α-ethinyl-Δ^{4}-oestrene-17β-ol, 17α-alkyl-Δ^{4}-oestrene-17β-ol and esters thereof with pharmaceutically acceptable acids.

However, for practical purposes, the last-mentioned, third group of effective progestogenes is less desirable since due to the lesser dissociation between the progestogenic effect and the ovulation-suppressing effect, the accurate dosing so as to achieve the desired progestogenic effect without suppression of ovulation is rather difficult.

If the progestogenes which may be utilized according to the present invention are in the form of esters, it is possible to utilize all physiologically active and pharmaceutically acceptable straight-chain or branched esters, for instance the acetates, valerates, butyrates, caproates, oenanthates, undecylates, etc. It is possible thereby that the ester-forming acid residue may also be substituted in conventional manner, for instance with one or more halogen atoms, hydroxyl, carbonyl, keto or amino groups.

As pointed out above, by proceeding in accordance with the present invention and administering the progestogene between the fifth and eighth day, preferably between the fifth and seventh day, after the start of the menstrual cycle, a contraceptive effect can be obtained which will last for at least one menstrual cycle, and by suitably increasing the dose and/or utilizing a long-lasting progestogene, it is also possible to achieve a contraceptive effect for longer periods of time, such as for instance for three to four months, or even longer.

Particularly with respect to the progestogenes of the first group (progestogenes which do not have any pituitary hypothalamic-inhibiting effect) and generally also with respect to progestogenes of the second group, i.e. progestogenes with substantial dissociation between the progestogenic and ovulation-suppressing effect, the effective dosage is generally between about 1 and 250 mg of the progestogene.

In many cases, particularly if the effect is to be limited to one menstrual cycle, a dosage of up to 100 mg will suffice.

For achieving a longer-lasting contraceptive effect by a single administration, it is possible and sometimes desirable to administer progestogenes of the first group in

amounts of up to 500 mg. For achieving a contraceptive effect for one menstrual cycle by administration of 19-nor-17α-hydroxyprogesterone caproate, the dose preferably will be between about 1 and 20 mg and most preferably about 2 and 5 mg, whereas by utilizing 17α-hydroxyprogesterone caproate preferably between 5 and 150 mg and most preferably about 50 and 100 mg will be administered.

It may be emphasized once more that the progestogene which is administered according to the present invention should be of a type and administered in an amount sufficient to inhibit the periovulatory changes of the cervical mucus and endometrium and possibly also of the tubal motility, which changes facilitate conception and/or nidation; however, by its type or dosage the administered progestogene should be incapable of suppressing hypothalamic/pituitary stimuli which induce ovulation.

The observed periovulatory changes of the cervical mucus include increased viscosity, certain crystallization phenomena (fern phenomena) and an increase in the quantity of cervical mucus. There exist a great number of other biochemical parameters, for instance glucose and protein content of the mucus, which indicate the cervical changes. In addition, the cervix is enlarged and certain changes of the endometrium occur which favor nidation. These indications of the periovulatory changes are well known to those skilled in the art.

The preferred method of administering the progestogene in accordance with the present invention is intramucularly. Implantation, while also possible, is less desirable due to the uncontrollable resorption of the progestogene, and subcutaneous administration is connected with the disadvantage that the effective agent, i.e. the progestogene may be resorbed too quickly.

It is an advantage of the present method that the contraceptive effect is achieved without suppression of ovulation and that with the exception of the periovulatory changes, particularly in the composition and condition of the cervical mucus, all biological and physiological processes of the female sexual cycle remain unaffected. Undesirable side effects such as are known to occur by oral application of combinations of progestogenic and estrogenic agents which achieve the contraceptive effect due to the ovulation-suppressing activity of the combination, were not observed when proceeding in accordance with the present invention.

The progestogenes are applied according to the present invention, preferably dissolved in a solvent suitable for parenteral administration. Such solvents and the manner in which the injectable solutions of active agents such as progestogenes are made, are well known to those skilled in the art. The progestogene is dissolved in the solvent, filtered under sterile conditions, and filled under aseptic conditions into ampoules of the desired size. Preferred solvents are oily solvents, for instance sesame oil or castor oil. However, other vegetable oils such as linseed oil, cottonseed oil, sunflower oil and peanut oil, olive oil, wheat germ oil and others are also suitable solvents. In order to improve the solubility of the progestogene, it is also possible to add, as known to those skilled in the art, diluents or solubilizing agents, for instance benzylbenzoate.

The vegetable oils which serve as solvents may also be replaced with synthetic solvents, for instance glycol, lactic acid ester, benzyl alcohol and the like. The manner in which the solution of the progestogene is formed and the composition of the pharmaceutical diluents and solvents is conventional, well within the skill of the art and thus does not require detailed discussion.

The following Examples are given as illustrative only, without, however, in any way limiting the invention to the specific details of the Examples.

EXAMPLE I

Five g 19-nor-17α-hydroxyprogesterone caproate are dissolved in sesame oil. The solution is made up with sesame oil to a volume of about 1000 ml, filtered under sterile conditions and filled in conventional manner under aseptic conditions into 1 ml ampoules. Thereafter, sterilization is completed for 2 hours at 120°C.

EXAMPLE II

Twenty g 19-nor-17α-hydroxyprogesterone caproate is dissolved in a mixture of 6 parts by weight castor oil and 4 parts by weight benzylbenzoate and this mixture is further added into the thus-formed solution until a total volume of 1000 ml is obtained. After filtration under sterile conditions, the thus-obtained solution is filled in conventional manner under aseptic conditions into 1 ml ampoules which are then further sterilized for 2 hours at 120°C.

EXAMPLE III

One-hundred fifty g 17α-hydroxyprogesterone caproate is dissolved in a mixture of 6 parts by weight castor oil and 4 parts by weight benzylbenzoate so as to obtain a total volume of 1000 ml. After filtration under sterile conditions, the solution is filled under aseptic conditions, in conventional manner, into 1 ml or 2 ml ampoules which, after closing, are then further sterilized for 2 hours at 120°C.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can by applying current knowledge readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspects of this invention and, therefore, such adaptations should and are intended to be comprehended within the meaning and range of equivalence of the following claims.

What is claimed as new and desired to be protected by Letters Patent is set forth in the appended claims:

1. In a single injection for at least one menstrual cycle method of preventing conception by inhibiting the periovulatory changes of the cervical mucus and endometrium required for conception and nidation without suppressing ovulation, the improvement which consists of parenterally administering a single injection for at least one menstrual cycle to a female of reproductive age on the fifth to eighth day of the menstrual cycle, of either (a) from about 1 to 20 mg of 19-nor-17α-hydroxyprogesterone caproate, or (b) from about 5 to 150 mg. of 17α-hydroxyprogesterone caproate, said progesterone when administered in such amount in said method being effective to prevent conception without effecting ovulation.

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