used in IVF/ICSI cycles. Although progesterone supplementation is used for luteal phase support in IVF/ICSI patients and can reduce uterine contractility, there is elevated uterine activity during the early luteal phase (day 2 or 3 post-retrieval) when transfer of cleavage-stage embryos is performed.

[0009] As uterine contractility is elevated during the early luteal phase (day 2 or 3 post-retrieval) when transfer of cleavage-stage embryos is performed, investigations assessing the impact of different interventions on uterine contractility for improving implantation have been conducted in the early luteal phase (day 2 and 3 post-retrieval transfer; hCG +4 days). Randomized controlled trials (Moon et al. 2004; Bernabeu et al 2006; Kim et al. 2008; Ng et al. 2014), quasi-randomized controlled trials (Moraloglu et al. 2010), retrospective studies in fresh and frozen embryo replacement cycles (Chou et al. 2011; Lan et al. 2012), or case studies in fresh and frozen embryo replacement cycles (Pierzynski et al. 2007; Liang et al 2009) reporting findings with compounds reducing uterine contractility, like atosiban (Kim et al 2008; Moraloglu et al. 2010; Ng et al. 2014), indomethacin (Bernabeu et al. 2006) and piroxicam (Moon et al. 2004) have been all conducted on day 2 or 3 post- retrieval, i.e., at the time of cleavage-stage embryo transfer.

[0010] A recent randomized controlled trial (Ng et al. 2014) compared the treatment outcome after administration of atosiban or placebo in IVF/ICSI patients followed by cleavage-stage embryo transfer on day 2 or day 3 post-retrieval. This large study was designed to determine whether the anecdotal evidence found in the previous smaller studies could be confirmed. This adequately-designed, large (N=800), double-blind, randomized, controlled trial found no significant increase in implantation or live birth rates with atosiban compared to placebo, as illustrated by live birth rates of 39.8% versus 38.0%, respectively (Ng et al. 2014). Atosiban administration on day 2 or day 3 post-retrieval therefore does not significantly increase implantation or live birth rates.

[0011] Consequently, improving implantation of transferred embryos remains one of the major challenges in assisted reproductive technologies (ART) treatment. It is an object of the present disclosure to improve implantation rates, thereby increasing pregnancy rates and live birth rates.

SUMMARY OF THE INVENTION

[0012] In one aspect, the present invention provides use of an oxytocin receptor antagonist in the manufacture of a medicament for increasing ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate, in a female subject undergoing embryo transfer as part of an assisted reproductive technology, wherein the antagonist is to be provided to the female such that the effect of the antagonist overlaps with the receptive endometrium stage in said female and the effect of the antagonist is present when the embryo has reached the blastocyst-stage. Disclosed is an oxytocin receptor antagonist for use in increasing

ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate, relative to control, in a female subject undergoing embryo transfer as part of an assisted reproductive technology, wherein the antagonist is provided to the female such that the effect of the antagonist is present when the female is in (or otherwise overlaps with) the receptive endometrium stage and/or when the effect of the antagonist coincides with the embryo reaching the blastocyst-stage. Preferably, the antagonist is provided such that it is released in the receptive

endometrium stage and/or when the embryo has reached the blastocyst-stage. Preferably, the antagonist is administered when the female is in the receptive endometrium stage and/or when the embryo has reached the blastocyst-stage. In certain examples, the antagonist is formulated for immediate release. In other examples, the antagonist is formulated as a sustained or delayed release formulation, such as a depot, and is administered prior to the receptive endometrium stage and/or when the embryo is still in cleavage stage such that the antagonist is released or continues to be released once the receptive endometrium stage is reached and/or the embryo has reached the blastocyst stage. Preferably, the antagonist is provided such that a therapeutically effective amount of the antagonist is present when the female is in (or otherwise overlaps with) the receptive endometrium stage and/or when the effect of the antagonist coincides with the embryo reaching the blastocyst-stage.

[0013] In preferred examples, the receptive endometrium stage corresponds to:

a) between LH+6 days and LH+9 days, preferably between LH+6 days and LH+8 days, most preferably on day LH+7 of a natural ovulation cycle;

b) between hCG+6 days and hCG+9 days, preferably between hCG+6 days and hCG+8 days; most preferably on day hCG+7 of an induced ovulation cycle;

c) between day 4 and day 7, preferably between day 4 and day 6, more preferably on day 5 or 6, most preferably on day 5, of luteal phase support, wherein luteal phase support begins the day following oocyte retrieval in an IVF cycle, preferably wherein the female has undergone ovarian stimulation; or

d) between day 4 to day 9, preferably between day 5 to day 7, more preferably on day 5 or day 6 of luteal phase support, preferably in preparation for frozen embryo transfer or third party IVF, and preferably wherein luteal support begins after the endometrium is primed for at least 6 days with exogenous oestrogen.

[0014] Preferably, luteal phase support comprises supplementation with progesterone, human chorionic gonadotropin, estradiol and progesterone, progestins and/or gonadatropin releasing hormone (GnRH) agonists.

[0015] Accordingly, the disclosure provides oxytocin receptor antagonists which can be used to prepare medicaments for increasing ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate, in a female subject undergoing embryo transfer as part of an assisted reproductive technology. Also encompassed by the disclosure are uses of oxytocin receptor antagonist for the preparation of a medicament for use in a female undergoing transfer of a blastocyst-stage embryo. Preferably a medicament is administered such that its effect overlaps with the receptive endometrium stage and/or when the embryo has reached the blastocyst-stage. Preferably, an antagonist in a medicament is released in the female when the female is in the receptive

endometrium stage and/or when the embryo has reached the blastocyst-stage. Preferably, an antagonist is provided such that a therapeutically effective amount of the antagonist is present when the female is in (or otherwise overlaps with) the receptive endometrium stage and/or when the effect of the antagonist coincides with the embryo reaching the blastocyst-stage.

[0016] The disclosure further encompasses methods for increasing ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate, in a female subject undergoing embryo transfer as part of an assisted reproductive technology, comprising administering to the female an oxytocin receptor antagonist such that the effect of the antagonist overlaps with the receptive endometrium stage and/or when the embryo (e.g., transferred embryo) has reached the blastocyst-stage. Preferably, methods are provided for increasing ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate in a female , said method comprising administering to the female prior to and/or following embryo transfer an oxytocin receptor antagonist such that a therapeutically effective amount of the antagonist is present during at least a portion of the receptive endometrium stage of the female and/or during at least a portion of the blastocyst-stage of a transferred embryo in the female, thereby increasing ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate relative to a control. In preferred examples, the methods further comprise transferring an embryo into the uterus, the uterine cavity or the fallopian tubes of a female, preferably wherein a blastocyst-stage embryo is transferred.

[0017] The disclosure further provides methods of implanting an embryo in a female subject, comprising transferring an embryo into the uterus, the uterine cavity or the fallopian tubes of a female and administering to the female an oxytocin receptor antagonist such that the effect of the antagonist overlaps with the blastocyst-stage of the embryo and/or the female is in the receptive endometrium stage. Preferably, an antagonist is provided such that a therapeutically effective amount of the antagonist is present when the female is in (or otherwise overlaps with) the receptive endometrium stage and/or when the effect of the antagonist coincides with the embryo reaching the blastocyst-stage.

[0018] Methods are also provided for implanting an embryo in a female subject, said method comprising transferring an embryo into the uterus, the uterine cavity or the fallopian tubes of a female and administering to the female an oxytocin receptor antagonist such that a therapeutically effective amount of the antagonist is present in the female during at least a portion of the receptive endometrium stage of the female and/or during at least a portion of the blastocyst-stage of the transferred embryo in the female

[0019] In preferred examples, the female is undergoing transfer of a blastocyst-stage embryo and the antagonist is administered to the female such that the antagonist is released to the female on the same day that the embryo is transferred. Preferably, the antagonist is administered between 2 hours prior to and 2 hours post embryo transfer (for example, in an immediate release formulation), preferably wherein the antagonist is administered twice, preferably wherein the first administration occurs around 45 minutes prior to embryo transfer and the second administration occurs around 60 minutes after the first administration. Preferably, a blastocyst-stage embryo has an expansion and hatching status of 3, 4, 5, or 6, more preferably wherein the blastocyst-stage embryo is a day 5 post-insemination embryo.

[0020] In preferred examples, the female is undergoing transfer of a cleavage-stage embryo and the antagonist is administered to the female such that the antagonist is released two or three days after the embryo is transferred. Preferably, a cleavage-stage embryo has at least 6 blastomeres and fragmentation of 20% or less, preferably wherein the cleavage-stage embryo is a day 2 or day 3 post-fertilization embryo.

[0021] In preferred examples, the antagonist is a selective oxytocin receptor antagonist or an vasopressin/oxytocin receptor antagonist. More preferably, the antagonist is a selective oxytocin receptor antagonist.

[0022] Preferably, the antagonist is barusiban. Preferably, barusiban is provided subcutaneously. Preferably, between 30-80 mg, more preferably 50 mg of barusiban is administered. In some examples, the female is undergoing transfer of a blastocyst-stage embryo and barusiban is administered to the female as a depot prior to the day of embryo transfer. Preferably, the female is undergoing transfer of a blastocyst-stage embryo and barusiban is administered to the female on the same day as embryo transfer. Preferably, 40 mg barusiban is administered subcutaneously about 15, 30, 45, 60, or 75 minutes (e.g., 45 minutes) prior to blastocyst stage embryo transfer and 10 mg barusiban is administered subcutaneously about 15, 30, 45, 60, or 75 minutes (e.g., 60 minutes) after the first administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figures 1A and 1B depict examples of oxytocin receptor antagonists.

[0024] Figure 2 depicts odds ratio for ongoing implantation rate by day of transfer for (BASIC) clinical trial.

[0025] Figure 3 is a graph of ongoing implantation rate by day of transfer for (BASIC) clinical trial.

DETAILED DESCRIPTION OF THE DISCLOSED EMBODIMENTS

Claims

1. Use of an oxytocin receptor antagonist in the manufacture of a medicament for increasing ongoing implantation rate, increasing ongoing pregnancy rate, increasing clinical pregnancy rate, and/or increasing live birth rate, in a female subject undergoing embryo transfer as part of an assisted reproductive technology, wherein the antagonist is to be provided to the female such that the effect of the antagonist overlaps with the receptive endometrium stage in said female and the effect of the antagonist is present when the embryo has reached the blastocyst-stage.

2. The use according to claim 1, wherein the receptive endometrium stage corresponds to:
a) between LH (luteinizing hormone) +6 to LH+9, preferably between LH+6 to LH+8, of a natural ovulation cycle;
b) between hCG (human chorionic gonadotropin) +6 to hCG+9, preferably between hCG+6 to hCG+8, of an induced ovulation cycle;
c) between day 4 to day 7, preferably between day 4 to day 6, of luteal phase support following oocyte retrieval, preferably wherein the female has undergone ovarian stimulation; or
d) between day 4 to day 9, preferably between day 5 to day 7, of luteal phase support, preferably wherein luteal support begins after the endometrium is primed for at least 6 days with exogenous estrogen.

3. The use according to claim 2, wherein the luteal phase support comprises supplementation with progesterone, estradiol and progesterone, human chorionic gonadotropin, progestins and/or gonadotropin releasing hormone (GnRH) agonists.

4. The use according to any one of the preceding claims, wherein the female is undergoing transfer of a blastocyst-stage embryo and the antagonist is to be provided to the female such that the antagonist is released on the day of embryo transfer.

5. The use according to claim 4, wherein the antagonist is to be administered to the female on the day of embryo transfer.

6. The use according to claim 5, wherein the antagonist is to be administered between 2 hours prior to and 2 hours post embryo transfer, preferably wherein the antagonist is to be administered twice,

preferably wherein the first administration occurs around 45 minutes prior to embryo transfer and the second administration occurs around 60 minutes after the first administration.

7. The use according to claim 5 or 6, wherein the blastocyst-stage embryo has an expansion and hatching status of 3, 4, 5, or 6, preferably wherein the blastocyst-stage embryo is a day 5 post-fertilization embryo.

8. The use according to any one of claims 1-3, wherein the female is to be undergoing transfer of a cleavage-stage embryo and the antagonist is to be provided to the female such that the antagonist is to be released two or three days after embryo transfer, preferably wherein the antagonist is to be administered to the female two or three days after embryo transfer.

9. The use according to claim 8, wherein the cleavage-stage embryo has at least 6 blastomeres and fragmentation of 20% or less, preferably wherein the cleavage-stage embryo is a day 2 or day 3 post-fertilization embryo.

10. The use according to any one of the preceding claims, wherein the antagonist is a selective oxytocin receptor antagonist or an vasopressin/oxytocin receptor antagonist.

11. The use according to claim 10, wherein the antagonist is barusiban.

12. The use according to claim 11, wherein barusiban is to be provided subcutaneously.

13. The use according to claim 11 or 12, wherein between 30-80 mg, preferably 50 mg, of barusiban is to be administered.

14. The use according to any one of claims 11-13, wherein the female is to be undergoing transfer of a blastocyst-stage embryo and barusiban is to be administered to the female on the same day as embryo transfer.

15. The use according to claim 14, wherein 40 mg barusiban is to be administered subcutaneously 45 minutes prior to embryo transfer and 10 mg barusiban is to be administered subcutaneously 60 minutes after the first administration.