FEMALE OBESITY IMPAIRS EMBRYO IMPLANTATION: RESULTS OF OUR DOUBLE DONATION CYCLES.
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Objective:
The effects of obesity on fertility outcome have been under controversy for a long time, however, recent studies show that there might be an increased infertility risk in women whose body mass index (BMI) is above 30 kg/m².
How obesity may affect the reproductive results can be explained from two different sides. Firstly, women who present ovulatory disorders in association with high BMI. Secondly, women who ovulate regularly but have decreased implantation and pregnancy rates.
In our study we tried to exclude the ovulatory disorders, to specifically assess the impact of obesity in implantation and pregnancy. Our aim was to analyze whether the reproductive outcome of those recipients of eggs and sperm donation was affected by their BMI.

Material and methods:
We did a retrospective cohort analysis of the egg and sperm donation cycles in our clinic from January 2010 until December 2012. We evaluated 68 cycles of recipients of eggs and sperm from normoweight donors.
We divided recipients into three different groups according to their BMI to analyze IVF laboratory and outcome parameters: group 1 with BMI <20 kg/m² (n=14); group 2 with BMI 20-24.9 kg/m² (n=42) and group 3 with BMI >25 kg/m² (n=12).
Recipients with recurrent miscarriages or implantation failure (except for chromosomal cause) and those with uterine factor (fibroids, adenomyosis or müllerian defects) were excluded from the study.
We looked at differences in pregnancy and clinical pregnancy.
We evaluated pregnancies until the fetal heart beat was detected.
Spanish law regulates egg and sperm donation, which must always be anonymous. Donors must be healthy men and women between 18 and 35 years old and with no family history of inherited diseases or chromosomal disorders. They must also have a negative screening for infectious diseases, a normal Karyotype and a normal psychological examination.
Female donors must also have a normal gynecological exam, including ovarian reserve tests, smear test and cervical culture.
Male donors must also have a normal sperm sample, with good post-thawing survival and a normal Cystic Fibrosis genotype. All male donors are re-tested for infectious diseases six months after they have given the sperm sample.
All our female donors underwent short ovarian stimulation protocols, with 225 IU/day of recombinant follicle-stimulating hormone (Gonal-F®) from the 3rd day of their cycle and a 0.25 mg dose of GnRH
antagonist (Cetrotide® or Orgalutran®) was added when the biggest follicle was 14 mm until the day of the ovulation induction. We controlled the stimulation by transvaginal ultrasound examinations, from the 5th day of stimulation and every 48 hours to monitor the ovarian response. The final oocyte maturation was done with two ampoules (0.2 mg) of GnRH-agonist triptorelin (Decapeptyl®) when at least two leading follicles had reached a mean diameter of 18 mm. Eggs were retrieved 36 hours after triptorelin administration.

Recipients underwent an endometrial preparation protocol that included estrogens in the form of 6 mg of Estradiol Valerate (Meriestra®) daily and after 7 to 10 days, endometrial thickness and pattern were controlled. If the endometrium showed a three-layer pattern and its thickness was at least 7 mm, estrogen therapy was continued at the same dose. If the endometrium was less than 7 mm, we increased the dose of estradiol, whether orally or using transdermal estradiol hemihydrate patches of 100mg (Estraderm®).

Recipients with preserved ovarian function also received a single intramuscular ampoule administration of 3.75 mg of triptorelin (Decapeptyl depot 3.75®) in the midluteal phase of the preceding cycle. The day of the pickup of the eggs, the recipient started with 200mg of micronized intravaginal progesterone (Progefok® or Utrogestan®) every 8 hours and continued with the estrogen therapy.

We used fresh oocytes for all cycles, and we fertilized them with ICSI. We transferred from one to three embryos on day 3 or 5 of development. We vitrified those extra embryos that were not replaced. Eleven to fourteen days after oocyte retrieval, a quantitative serum value of b-hCG was obtained. We considered a positive result when the value was higher than 10mUI/L, and repeated the test if the value was between 10 and 100 mUI/L to assess the b-hCG curve.

If the b-hCG value was positive, we performed a transvaginal ultrasound from 7 to 10 days after, and then we repeated the scan weekly until detection of an embryo heartbeat. Transdermal and/or oral estradiol and vaginal micronized progesterone were continued at the same dosage until the 12th week of pregnancy.

Outcome Measures:
We defined pregnancy as a positive b-hCG value in the first blood test for b-hCG detection. We considered clinical pregnancy when an embryonic sac was seen in ultrasound. Miscarriage was diagnosed when the pregnancy stopped before week 12 of pregnancy after the detection of the gestational sac(s) by ultrasound. Ectopic pregnancy was defined as a sac detected by ultrasound or laparoscopy out of the uterine cavity, when the b-hCG levels increased less than double every 48 hours or due to the patient's symptoms.

Statistics:
We divided patients into three groups, based on BMI as described above and considered the variables as proportions or means together with a confidence interval of 95%(IC 95%), which we calculated with Macro ICIP for SPSS. Statistically significant differences between the groups can be identified in cases without overlapping of the intervals.

Results:
We found no differences in age (41.8, 41.7 and 43.0 years), protocol and estrogen dose during endometrial preparation (89.4 mg, 87.3 mg and 81 mg) of the recipients among the three groups.

We found no differences in parameters of male and female donors (age, BMI, stimulation protocol and final triggering, number of mature oocytes, sperm motility at ICSI).

We observed similar fertilization rates and embryo quality. We replaced (1.8, 1.8 and 2 embryos) and cryopreserved (3.1, 1.7 and 2 embryos) the same average embryos in the three groups.
Pregnancy rate in Group 1 was 71.4% (CI 95%: 47.8%-95.1%), in Group 2 was 59.5% (CI 95%: 44.7-74.4%) and in Group 3 was 33.3% (CI 95%: 6.7%-60.0%). Clinical pregnancy rate in Group 1 was 64.3% (CI 95%: 39.2%-89.4%), in Group 2 was 47.6% (CI 95%: 32.5-62.7%) and in Group 3 was 33.3% (CI 95%: 6.7%-60.0%).

Miscarriage rates were similar in all the groups.

Conclusion:
BMI may interfere with embryo implantation in those women who undergo a double donation cycle, as a result of reduced uterine receptivity. Although our study could not find statistically significant differences among the three groups, there seems to be a trend towards a lower pregnancy rate in those recipients with a higher BMI. Further studies including more double donation cycles are needed to confirm these results.