Outcome of gestational surrogacy according to IVF protocol

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Abstract

Purpose Surrogacy remains the only option for having a biologic child for a unique population of women with severe medical conditions. However, no study has looked at surrogacy outcome as a result of the type of ovarian stimulation of the intended mother [controlled ovarian stimulation (COH), modified natural cycle (MNC), and in vitro maturation (IVM)] for oocyte retrieval.

Methods This is a retrospective study, including all intended mothers and gestational carriers in a tertiary, university affiliated, medical center, from 1998 to 2016.

Results Fifty-two women underwent 252 oocyte retrieval cycles. The pregnancy outcome of 212 embryo transfer cycles (64 gestational carriers) was reviewed according to the origin of the embryo. The number of retrieved oocytes was significantly higher following COH ($n = 132$) compared with IVM ($n = 58$) and MNC cycles ($n = 62$) ($p = 0.013$ and $p < 0.0001$, respectively). Pregnancy rates for embryos transferred according to each protocol were similar. All pregnancies that ended in live births when oocytes from IVM cycles were used derived from transfers of retrieved mature and mixed

mature and immature oocytes. Pregnancies that involved embryos derived solely from immature oocytes that further matured in vitro and were transferred to gestational carriers were unsuccessful.

Conclusions MNC protocol is a good option to achieve pregnancy for intended mothers using gestational surrogacy who have contraindications to COH. The yield of IVM cycles in which immature oocytes are retrieved is inconclusive.

Keywords Gestational surrogate · Intended mothers · In vitro maturation · Modified natural cycle

Introduction

Surrogacy offers an alternative way of conception for women who are unable to conceive a child naturally [1, 2]. The process involves one woman (gestational carrier) carrying a child for another person or couple (commissioning person/couple) and based on an agreement that the infant will be relinquished to the commissioning person/couple after birth. The common indications for surrogacy include the absence of a uterus, repeated in vitro fertilization (IVF) failures, medical conditions for which pregnancy is contraindicated (e.g., severe thrombophilia, antiphospholipid syndrome, end stage renal diseases or vasculitis), single males, and same sex male couples [3].

The emerging technique of uterine transplantation may offer a future solution in cases of intended mothers without a uterus [4]. Gestational surrogacy remains the only alternative to have offspring from their own oocytes among women with medical conditions for whom pregnancy is contraindicated [5]. In some of these cases (i.e., catastrophic antiphospholipid syndrome, active systemic lupus erythematosus, previous cerebral vascular hemorrhage, and pulmonary emboli), the

Capsule A modified natural cycle protocol is suitable for women for whom controlled ovarian stimulation is contraindicated. The yield of in vitro maturation cycles with retrieval of immature oocytes is unclear.

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intended mothers have contraindications for regular gonadotropins doses for ovarian stimulation in order to avoid any significant increase of estradiol levels as well as the risk for ovarian hyperstimulation syndrome. In these cases, the options to achieve oocytes are either minimal stimulation with mild doses of gonadotropins, in vitro maturation (IVM), or modified natural cycles (MNC) [6].

Earlier studies compared the outcome of gestational carrier cycles in women with and without a uterus [7, 8], or those using autologous vs. donor oocytes [9], but there are none on the outcome according to the origin of the oocytes/embryo (controlled ovarian stimulation [COH], MNC, and IVM cycles). To address this issue, we evaluated the outcome of surrogacy cycles according to the origin of the oocyte/embryo over an 18-year period in a single academic medical center.

Materials and methods

The medical records of all women who underwent gestational surrogacy cycles (both intended mothers and gestational carriers) in our medical center from 1998 and 2016 were reviewed. The collected data included demographics, reason for gestational surrogacy, cycle stimulation protocol, number of oocytes retrieved, number of fertilized oocytes, number of IVF cycles in which fresh embryos were transferred, number of IVF cycles in which frozen-thawed embryos were transferred, number of embryo transferred, positive beta-human chorionic gonadotropin (hCG), clinical pregnancy rates, miscarriage rates, and number of live births.

IVF protocols

COHs consisted of the long GnRH agonist suppressive protocol, the flare GnRH agonist protocol, or the GnRH antagonist protocol. The MNC protocol was based on natural cycles with 2–3 ampules of human menopausal gonadotrophin (Menogon or Menopure, Ferring) and co-administration of GnRH antagonist supplementation (0.25 mg/day; Cetorelix, Cetrotide, (MERCK started when a follicle of 13 mm was identified [10, 11]. hCG was administered for final oocyte maturation 36 h prior to oocyte retrieval in all three stimulation protocols.

The IVM protocol was described in detail elsewhere [12]. Briefly, after baseline evaluation of an ultrasound (US) scan and the acquisition of a hormonal profile on days 2–4 of the menstrual cycle, a second evaluation was carried out between days 6 and 8 of the menstrual cycle. The US scan and blood tests were repeated every 1–3 days until the endometrial thickness was >6 mm and the leading follicle was 12–14 mm in size. Oocyte retrieval was performed 36 h later with or without hCG priming [13]. When the endometrium was not thick enough and the women did not have any contraindication to

mild hormonal stimulation, mild stimulation with 75 IU follicle-stimulating hormone (FSH; Gonal-f Pen; Serono, London, United Kingdom) was given for 3–5 days, and hCG for final follicular maturation was administered 36 h before retrieval (“IVM with short gonadotropin stimulation”) [14]. The gestational carrier’s endometrium was prepared with vaginal estradiol (Estrofem, Novo Nordisk, Denmark, 2mg bid). ICSI was performed in all IVM cycles and in cases of male factor infertility.

Positive beta-hCG was documented 12 days after embryo transfer. Clinical pregnancy was defined by the presence of a gestational sac and visualization on US of at least one fetal heartbeat 4 weeks after embryo transfer. Miscarriage was defined as no fetal heartbeat 5 weeks after embryo transfer. Positive beta-hCG, clinical pregnancy rates, miscarriages, and ongoing pregnancies/deliveries were given as percentages of total transfers.

Statistics

Statistical analysis was performed using generalized linear mixed models after square root transformation to achieve normal distribution. Models were adjusted for possible confounders (age of the intended mother and reason for surrogacy). Results are presented as means $\pm$ SD. $P < .05$ was considered significant. Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 23.

Ethics

The study was approved by our institutional review board.

Results

Participants

Between 1998 and 2016, 52 intended mothers underwent 252 oocyte retrieval cycles in our program. The embryos were transferred to 64 gestational carriers in 212 IVF cycles. The mean age $\pm$ SD of the intended mothers was 33.5 ± 3.0 years (range 22–41). Out of the 52 women who used a gestational carrier, 21 (40.3%) underwent the procedure due to the lack of a uterus (either congenital or acquired), 3 (5.8%) due to recurrent IVF failure, and 28 (53.9%) due to maternal disease with a contraindication to conception (e.g., severe thrombophilia, antiphospholipid syndrome, rheumatoid diseases, end stage renal diseases, vasculitis, or status post renal and pancreas transplantation). Of the 252 retrieval cycles, 132 were by the COH protocol, 62 by the modified natural cycle protocol, and 58 by the IVM protocol. Indications for IVM cycles were severe thrombophilia ($n = 32$), status post renal and pancreas transplantation ($n = 6$), status post severe pre-eclampsia and

nephropathy ($n = 3$), tuberous sclerosis with bleeding angiolioma ($n = 4$), multiple sclerosis ($n = 6$), and cystic fibrosis with low protein S levels ($n = 7$). Generalized linear mixed models showed no association between reason for surrogacy and the number of oocytes that were retrieved/fertilized. Table 1 compares the outcome of the retrievals according to the three protocols.

Complete stimulation data were available for 54 out of the 58 cycles (Table 2) in the IVM group. Neither short gonadotrophin stimulation nor hCG triggering was used in 22 cycles (40.7%), and no gonadotrophin was used in 10 cycles, but they were triggered by hCG (18.4%) and both gonadotrophin stimulation and hCG triggering were given in the other 22 cycles (40.7%).

Cycle outcome

The mean age $\pm$ SD of the 64 gestational carriers was 31.9 ± 4.0 years (range 22–40). Nine of them (14.3%) were married, 13 (20.4%) were single, and 42 (65.3%) were divorced. The gestational carriers had 1.8 ± 0.94 (range 0–4) biological children. Of the 212 cycles in which embryos were transferred to the gestational carriers, the embryos were achieved following the COH protocol in 152 cycles (71.9%), following the MNC protocol in 17 cycles (8.1%), and following the IVM protocol in 43 cycles (20%). Generalized mixed models showed that the number of embryos transferred, the stimulation protocol, and the number of fresh/thawed embryos were not associated with the chances to conceive. The numbers of fresh cycles, frozen cycles, number of embryos transferred, positive β -hCG, clinical pregnancy rates, and ongoing pregnancies/deliveries are presented in Table 3. The ongoing pregnancy rate was almost doubled following COH compared to the MNC protocol or IVM (9 vs. 6.7 and 5.5%,

respectively), although the difference did not reach a level of significance.

In a sub-analysis of the embryos that originated after IVM (Supplementary Table 1), embryos developed from oocytes that matured in vitro in 25 out of 43 transfer cycles (58%). In the remaining 18 cycles, the transferred embryos were derived solely from mature oocytes retrieved during IVM cycles (6/43) or a combination of embryos derived from mature oocytes that were retrieved during IVM and from immature oocytes that were matured in vitro and further fertilized and developed to embryos (12/43 cycles). Of the cycles in which the transferred embryos originated from retrieved immature oocytes only, three ended in pregnancy but none in ongoing pregnancy or delivery. Moreover, of the IVM cycles in which transferred embryos originated from solely matured or mixed mature and immature oocytes, pregnancy was achieved in three cycles, of which two pregnancies ended in term delivery of healthy babies.

Discussion

The findings of the current study demonstrated that the best prognosis for gestational surrogacy cycles was achieved following the COH protocol. Moreover, while the IVM protocol yielded significantly higher numbers of retrieved oocytes compared to the MNC protocol, no ongoing pregnancy was achieved following the transfer of embryos that were originated solely from immature oocytes that were matured in vitro.

A modified natural protocol with minimal ovarian stimulation has been used preferentially in our department for women undergoing IVF who had contraindications to even mild ovarian stimulation because of maternal medical conditions. While the reported pregnancy rates in the literature following MNC are relatively low, i.e., 6–10% [15, 16], pregnancy rates were

Table 1 Comparison of oocyte retrieval cycles in intended mothers among those undergoing controlled ovarian stimulation, modified natural cycles, or in vitro maturation ($n = 252$)

	Controlled ovarian stimulation ($n = 132$)	Modified natural cycle ($n = 62$)	In vitro maturation ($n = 58$)	P^a
Patient's age, years (mean $\pm$ SD)	33.5 ± 4.8	33.7 ± 2.9	33.7 ± 2.4	NS
Cycles due to lack of uterus (%)	85 (64.1%)	0	1 (1.7%)	
Cycles due to medical conditions (%)	36 (27.5%)	62 (100%)	57 (98.3%)	
Cycles due to recurrent abortions (%)	11/132 (8.4%)	0	0	
Cycles with male factor comorbidity	14/132 (10.6%)	2/62 (3.2%)	7/58 (12.0%)	
Cycles with no oocytes retrieved (%)*	3/132 (2.3%) a	11/62 (17.7%) b	6/58 (10.3%)	0.001
Number of oocytes retrieved (mean $\pm$ SD)**	7.4 ± 4.6 a	1.1 ± 0.8 b	5.9 ± 4.0 c	0.001
Number of fertilized oocytes (mean $\pm$ SD)***	5.0 ± 0.8 a	0.8 ± 0.7 b	2.8 ± 2.3 c	0.001
Cycles with ICSI (%)	34/129 (26.4%)	26/51 (51%)	52/52 (100%)	

* P values are 0.001 for a–b; ** P values are 0.001 for a–c and 0.013 for b–c; *** P values are <0.001 for a–c and 0.002 for b–c

^a Stimulation type significantly affected the number of oocytes retrieved, fertilized, and number of oocytes without oocytes retrieved. P values are derived from generalized linear mixed models after square root transformation to achieve normal distribution

Table 2 Characteristics of in vitro maturation cycles ($n = 54$)

	IVM with short gonadotrophin stimulation ($n = 22$)	Natural cycle IVF with early triggering combined with IVM ($n = 10$)	IVM without triggering ($n = 22$)
Woman's age, years (mean $\pm$ SD)	34.3 $\pm$ 1.3	32.5 $\pm$ 2.7	33.1 $\pm$ 2.7
Number of oocytes retrieved (mean $\pm$ SD)	7.0 $\pm$ 3.8	6.2 $\pm$ 3.3	5.1 $\pm$ 4.6
Cycles with MII oocytes retrieved	19 (86.4%)	2 (20%)	7 (31.8%)
Number of embryos suitable for transfer or freezing (mean $\pm$ SD)	2.9 $\pm$ 1.8	2.1 $\pm$ 2.1	1.7 $\pm$ 2.0

IVM in vitro maturation, IVF in vitro fertilization, SD standard deviation

17.6% for intended mothers undergoing this protocol in our study. A possible explanation for this discrepancy can be the difference in patients' age and ovarian reserve. Most of the studies to date have published the results of MNC in patients of all ages with low ovarian reserve, while we describe the outcome of a young population (<35 years old) with adequate ovarian reserve. Our results are in line with those of Schimberni et al., who showed pregnancy rates of 18.1% among patients <35 years old undergoing IVF with an MNC protocol [16].

Among the disadvantages of MNC are cancellation rate due to premature pre-mature luteinizing hormone surges and retrieval of only one oocyte [17]. According to our data, cancellation rates were significantly higher for women undergoing MNC compared with COH. While MNC is much cheaper than COH per treatment cycle, several cycles of oocyte retrievals may be required for MNC compared with one cycle for COH or IVM for intended mothers who use gestational surrogates since only one oocyte is usually retrieved with MNC.

IVM is a well-established way to retrieve a high number of oocytes in women with contraindication to ovarian stimulation [18]. However, it might still be associated with a lower live birth and higher miscarriage rates compared with conventional IVF with COH [19, 20]. One of the possible

explanations is that maturation of the oocytes in vitro does not adequately deal with both the nuclear and cytoplasmic changes, which can affect embryo quality [21]. Our IVM group consisted of several protocol modifications, i.e., either with or without mild gonadotropin stimulation or hCG triggering. Recently, Dahan et al. [14] suggested a new classification of IVM, according to which our IVM group would consist not only of "true" IVM cycles but also of modified natural IVF cycles with early hCG triggering combined with IVM and natural cycle IVF with early hCG triggering combined with IVM. Out of the six pregnancies achieved in our IVM group, three were achieved in cycles in which the transferred embryos were derived solely from retrieved mature oocytes or both mature oocytes and oocytes that were matured in vitro. The other three pregnancies were derived from embryos matured by IVM without gonadotropin stimulation or hCG triggering and they all ended in either chemical pregnancies ($n = 2$) or first trimester missed abortion ($n = 1$).

Our study has several limitations. First, more embryos were transferred in the COH group compared with the MNC group. Although the difference was not statistically significant, it might be important from a clinical point of view and possibly affect the pregnancy rates and outcomes. Second, although the analysis was controlled for patients' age, there are still possible confounders, such as ovarian reserve, systemic diseases,

Table 3 Outcome of embryo transfer to gestational carriers according to the origin of the embryo ($n = 212$)

	Controlled ovarian stimulation protocol ($n = 152$)	Modified natural protocol ($n = 17$)	In vitro maturation protocol ($n = 43$)
Gestational carrier's age, years	31.7 $\pm$ 4.3	31.4 $\pm$ 2.7	32.2 $\pm$ 3.4
No. of fresh cycles (% of transfers)	79 (52%)	7 (41.2%)	29 (67.4%)
No. of cryopreserved cycles (% of transfers)	71 (46.7%)	9 (52.9%)	10 (23.3%)
No. of embryos transferred (mean $\pm$ SD)	2.3 $\pm$ 0.7	1.4 $\pm$ 0.5	2.3 $\pm$ 0.7
No. of positive hCG (% of transfers)	31 (20.5%)	3 (17.6%)	6 (14.2%)
No. of clinical pregnancies (% of transfers)	24 (14.3%)	2 (6.7%)	3 (8.2%)
No. of miscarriages (% of transfers)	8 (5.3%)	0	1 (2.7%)
No. of ongoing/delivered (% of transfers)	16 (9%)	2 (6.7%)	2 (5.5%)

hCG human chorionic gonadotropin, SD standard deviation

and male factor infertility that might have affected both female fertility and pregnancy rates. Last, all IVM cycles used ICSI for fertilization, which might affect IVF outcome.

These results are still preliminary and they are limited due to the small sample sizes. However, since the IVM protocol required more expertise on the part of both the physicians and the laboratory compared with modified natural cycles, due to the advantage of COH over IVM, IVM should be considered only in selected cases. The value of its use in the setting of gestational surrogacy warrants further studies to determine its relative benefit among intended mothers who plan to use gestational surrogacy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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