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Original article

Complications related to *in vitro* reproductive techniques support the implementation of natural procreative technologies

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Abstract. *Background and aim:* Infertility affects ~20% of the couples in the world. Assisted reproductive technologies (ARTs) are currently the most common treatment option for infertility. Nevertheless, ARTs may be associated with complications for mothers and/or offspring. Natural procreative technology (NaProTechnology) is a natural treatment which minimizes these risks by seeking to identify the causes of infertility to enable better treatments. This narrative review summarizes the complications related to ARTs and clarifies how the NaProTechnology approach can help ARTs to achieve better results or be used in alternative to ARTs. *Methods:* Data in the literature indicate that NaProTechnology is a natural approach for treating infertility. *Results:* The percentage of live births obtained by NaProTechnology is similar to that of ARTs. *Conclusions:* An extensive search for the genetic defects causing infertility or subfertility through genetic testing can help both ARTs and NaProTechnology to achieve successful pregnancies. By discovering the underlying causes of infertility, genetic tests enable better family counseling, like the implications of transmitting risk- and disease-alleles to future generations. (www.actabiomedica.it)

Key words: assisted reproductive technology, genetic infertility, NaProTechnology

Introduction

Human fertilization involves the fusion of two functionally and morphologically different haploid cells (spermatozoon and oocyte) to generate a new diploid organism. In the case of women of fertile age, infertility is defined as failure to become pregnant after 12 months of regular unprotected intercourse.

A systematic analysis, published in 2012, of 277 surveys revealed that among women aged 20–44 years, exposed to unprotected intercourse, 1.9% were unable to achieve a live birth, and among women with at

least one live birth, 10.5% were unable to have another child (1). Assisted reproductive technology (ART) treats infertility and obtains a high pregnancy rate (2). The most commonly used ART techniques are *in vitro* fertilization, intra-cytoplasmic sperm injection, controlled ovarian hyperstimulation and embryo transfer (3). Around the world, more than 500000 newborns are conceived through ART every year (4). Data in the literature indicates that ARTs may be associated, for example, with an increased rate of ovarian hyperstimulation syndrome and multiple pregnancies in mothers, and preterm birth, low birth weight, tumors and genetic/epigenetic alterations in offspring. The routine ART approach includes a set of basic clinical investigations aimed at identifying broad causes of infertility, although, recently, it is starting to focus on the increasing number of genetic factors known to impact human fertility (5).

Unlike ART, restorative reproductive medicine, such as natural procreative technology (NaProTechnology), focuses on improving gynecological health and restoring optimal reproductive function through medical and surgical reproductive procedures (6). This approach implies that if the cause of infertility is identified and treated, normal reproductive function can be restored and pregnancy can be achieved by normal intercourse without running the risk of ART-related complications (6). In addition, identification of the genetic cause of infertility in a couple gives adult offspring the opportunity to know key genetic information regarding their reproductive risk, and perhaps prevention and treatment options.

This narrative review summarizes current known ART-related risks for mothers and offspring, and illustrates the principles and treatment options of NaProTechnology.

Methods

Review of the literature

For this narrative review, PubMed was searched using the following search string: "infertility" AND "assisted reproductive technology" OR "NaProTechnology". We evaluated articles published until August 2019 written in English. We then only selected articles related to complications associated with ART and to the NaProTechnology approach.

Results

ART-related complications for mothers

A study performed in the Netherlands showed that the mortality rate in ART pregnancies is greater than the mortality rate in normal pregnancies: 42 deaths per 100000 against 6 deaths per 100000, respectively (7).

ART can increase the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies (8,9). To retrieve more oocytes, ART frequently resorts to controlled ovarian stimulation, which improves outcome in terms of likelihood of getting pregnant, but at the same time may increase the risk of OHSS (10). This risk may range from 3% to 10% in ART cycles, and can reach 20% in high risk women (11). OHSS can cause serious issues and complications for pregnant women, and if not treated promptly, can lead to miscarriage or loss of ovarian function (12).

Another major complication associated with ART is increased risk of extra uterine/ectopic pregnancies. The rate of ectopic pregnancies after ART ranges from 1% to 8.6%, whereas with normal conception it ranges from 1% to 2% (13).

According to the "Million Women Study" performed in the United Kingdom, the current practice of hormone replacement therapy is linked to a high risk of fatal breast cancer (14). Several population studies have demonstrated that infertile women undergoing hormonal stimulation for multiple oocyte production have a higher risk of breast cancer, especially when stimulation is with clomiphene or in the case of young women undergoing ART (15).

Another complication that may affect the health of women is hypertension, which is the cause of about 14% of maternal deaths (16). Specifically, women undergoing ART have double the risk of developing hypertension compared to pregnant women who conceived naturally (17).

ART-related complications for fetus and newborn

ART is associated with increased risk of low birth weight, preterm delivery, miscarriage and perinatal mortality (18). The higher risk of miscarriages embryos in the early phases of ART pregnancies may be due to chromosomal abnormalities or other genomic and epigenomic alterations (19). According to a meta-analysis that compared 12283 ART-conceived singleton infants with 1.9 million normally conceived singleton infants, the former showed a significantly higher rate of perinatal mortality, preterm births, small-for-gestational-age status and low/very low birth weight (20). In another recent analysis, researchers were unable to establish a significant association between ART and preterm births, although they found a higher risk of *placenta previa*, *abruptio placentae*, preeclampsia and caesarean delivery (21). The frequency of stillbirths is also higher in ART pregnancies (16.2/1000) than natural pregnancies (2.3/1000) (22).

Long-term potential complications of ART

A tripled risk of neural tube defects, gastrointestinal atresia, omphalocele and hypospadias was found in a cohort of Scandinavian newborns conceived by ICSI. It has been surmised that the increased risk of gastrointestinal atresia and monozygotic twinning after ART is a direct consequence of the procedure. Others have suggested that the higher risk of hypospadias after intracytoplasmic sperm injection could be related to paternal subfertility determined by a specific genetic background (23).

It was recently also established that ART may cause epigenetic defects resulting in various human disorders (24). In a Japanese study, researchers found that Beckwith-Wiedemann, Angelman, Prader-Willi and Silver-Russell syndromes are more frequent in babies conceived by ICSI and IVF than in spontaneously conceived babies (25).

Administration of exogenous hormones may affect fetal growth and organ differentiation, leading to increased risk of endocrine-sensitive cancer in later life (26). Some studies suggest a possible increased risk of cancer, including neuroectodermal tumors, malignant lymphoma and hepatoblastoma, in children conceived by ART (27-29).

Discussion

NaProTechnology and ART

The main treatment option for infertility is currently ART. It is available worldwide, but is expensive and associated with some risks for the mother and child (Table 1) (30).

An American surgeon and gynecologist, Dr. Thomas Hilger, proposed a method for natural procreation called NaProTechnology, which takes a natural approach to regulating fertility. NaProTechnology seeks to treat infertility with surgical, endocrinological or pharmacological personalized and targeted therapies (46). NaProTechnology also focuses on locating the fertility peak to optimize the chances of conception and offers couples an opportunity to conceive by a natural intercourse (40).

The approach follows the rules of the Creighton Model Fertility Care System (CrMS) that evaluates biochemical and hormonal parameters and organ dysfunction. The parameters include short/variable luteal phases, uterine bleeding, decreased levels of progesterone and estrogen, and reduced production and release of cervical mucus (30).

In 1972, Billings and collaborators successfully tested a NaProTechnology approach by getting women themselves to notice the signs and symptoms, like cervical mucus, that indicate the ovulatory period and fertility peak (47).

Another study, published in 2008, showed that 1239 infertile couples, treated with NaProTechnology, had a live birth rate similar to that of the ART-treated group (30). In the first step, couples were educated to identify fertile days according to the CrMS; medical treatment, including clomiphene administration, was given to 75% of couples. The results showed that 52.8% of couples treated with NaProTechnology had a live birth within 24 months (30).

Another method developed to predict the probability of conception is based on the Bayesian statistical method. This method evaluates the menstrual cy-

Table 1. Characteristics of ART and NaProTechnology compared to normal pregnancies

Parameter	ART	NaProTechnology	Reference
Cost	↑↑↑	↑	31
Perinatal death rate	↑	≈	30,32
Extra-uterine pregnancy risk	↑	≈	13,30
Ovarian hyperstimulation syndrome risk	↑	≈	9,30
Genetic mutations risk	↑	≈	33,34
Epigenetic alterations risk	↑	≈	35-37
Chromosomal anomalies risk	↑	≈	33,34,37
Breast/ovarian cancer risk	↑	≈	15,30,38
Maternal mortality rate	↑	≈	7,30
Invasive procedures frequency	↑	≈	39,40
Low birth-weight risk	↑	≈	6,41
Long-term side effects risk	↑	≈	42-44
Genetic screening	Variable	Extensive	19,45
Genetic counseling	Variable	Extensive	19,45
Birth defects rate	↑	≈	30,44

cle, and the mucus level and composition in order to increase the chances of conception by minimizing the frequency of intercourses (48). This simple method is based on mucus parameters and conventional markers of ovulation, such as serum hormone values and body temperature increase (49). It was estimated that outside the mid-cycle interval (day 7 to 20) the chance of conception is close to zero (49), and is directly linked to the type of mucus, classified from the most to the least fertile type in the mid-cycle interval (49). These natural fertility regulation methods may help couples recognize the most fertile period and clinicians to identify any abnormality that could be linked with infertility (50).

NaProTechnology and genetics

Infertility appears to be genetically determined in about 50% of cases (51). The burden of deleterious genetic variants in human reproduction is also documented by the fact that genetic diseases account for 20% of neonatal mortality and 10% of neonatal hospitalization (52).

NaProTechnology and ART have the same goal, namely to improve the chance of achieving pregnancies that produces healthy offspring. However, there is evidence to suggest that ART can amplify genome instability and therefore affect the chances of conceptions carrying potentially deleterious *de novo* mutations (53). Accordingly, several follow-up studies of children conceived by ART have proposed that ART is associated with an increased frequency of genetic and epigenetic abnormalities, as previously stated (see Long-term potential complications of ARTs).

Importantly, since genetic sequencing is now less costly and advances have been made in the interpretation of bioinformatic output, extensive genetic screening of couples for genetic factors predisposing to serious and/or neonatal/children's diseases will soon be plausible by next generation sequencing (NGS). This approach could offer couples the opportunity to discover whether they risk transmitting serious or unexpected Mendelian pathologies not indicated by their family history. Couples with fertility problems could be the first to take advantage of NGS screening. Another important point to highlight is that if a couple does not know it carries a genetic mutation that causes infertility and ART enables them to conceive, they are postponing the problem until the next generation. In such cases, NaProTechnology is facilitated by diagnostic methods that offer a couple a more complete picture of their reproductive risks and therefore a more

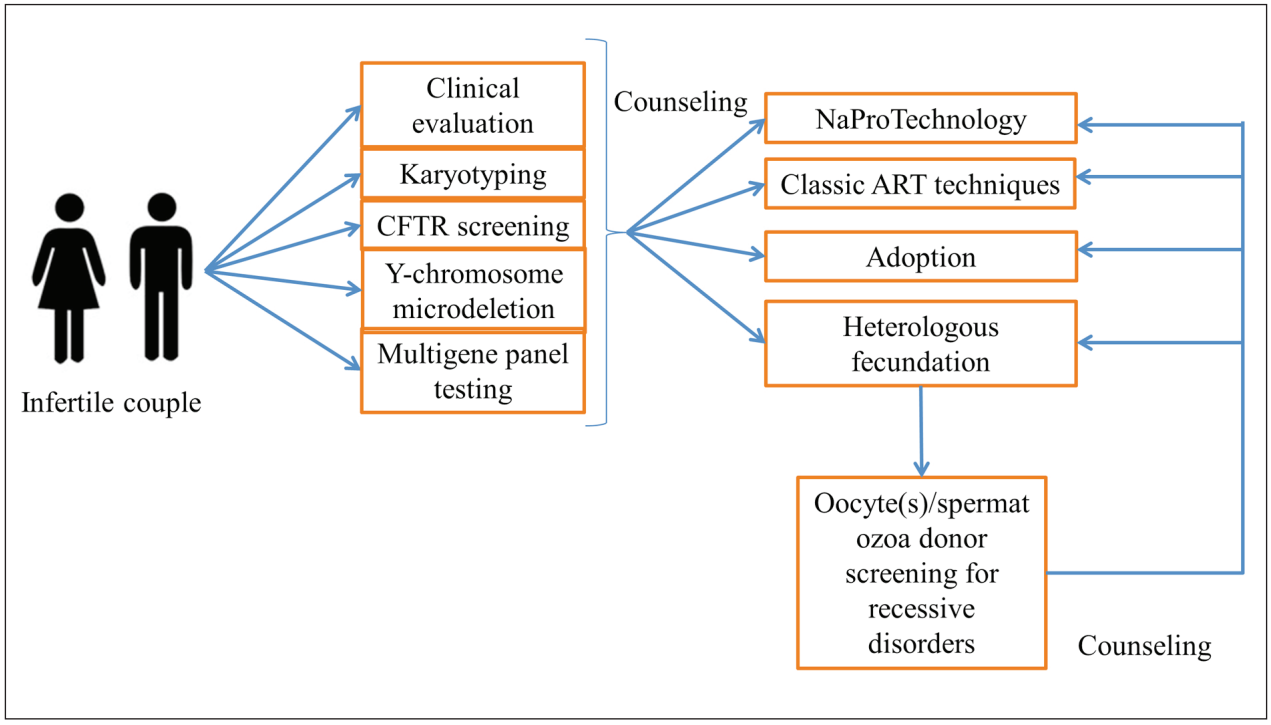

Figure 1. Flowchart for the counseling, diagnosis and treatment in couples with infertility

conscious choice between natural reproduction, ART or adoption.

In conclusion, it used to be prohibitively expensive for couples to undergo a detailed diagnostic phase including extensive genetic study, but it is now relatively accessible with NGS. Here, we propose a list of genes known to cause Mendelian infertility that could be included in a diagnostic panel for couples with idiopathic infertility (Figure 1, Table S1) (45,52,54-59).

Conclusions

NaProTechnology is an approach that optimizes natural reproduction in cases of infertility with the aim of minimizing risks for mothers and offspring. NaProTechnology aims to improve the natural reproductive cycle of the couple, thereby avoiding risks related to embryo handling and hormone therapies. Knowing the underlying causes of infertility can help couples to achieve better outcomes. In this scenario, the use of NGS to assess couples with reduced fertility is making diagnosis easier, as in other areas of medicine with a significant genetic burden. Finally, NGS makes it possible to consider the pros of extensive pre-conceptive genetic screening of couples to identify alleles associated with risk of early severe/lethal disorders, and to use this information for better prevention and monitoring of reproductive risk, also in the long term.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Table S1. Genes associated with male and female infertility (https://www.omim.org/)

Female infertility

Gene	Inheritance	OMIM gene ID	OMIM phenotype	OMIM phenotype ID	Clinical Features
HFM1	AR	615684	POF9	615724	Amenorrhea
FIGLA	AD	608697	POF6	612310	Small/absent ovaries, follicles absent, atrophic endometrium
FOXL2	AD	605597	POF3	608996	Hypoplastic uterus and ovaries, follicles absent, secondary amenorrhea
MSH5	AR	603382	POF13	617442	Oligomenorrhea, atrophic ovaries, follicles absent
STAG3	AR	608489	POF8	615723	Primary amenorrhea, ovarian dysgenesis
NOBOX	AD	610934	POF5	611548	Secondary amenorrhea, follicles absent
NR5A1	AD	184757	POF7	612964	Irregular or anovulatory menstrual cycles, secondary amenorrhea, dysgenetic gonads, no germ cells
ERCC6	AD	609413	POF11	616946	Secondary amenorrhea
SYCE1	AR	611486	POF12	616947	Primary amenorrhea, small prepubertal uterus and ovaries, no ovarian follicles
MCM8	AR	608187	POF10	612885	Absent thelarche, primary amenorrhea, no ovaries, hypergonadotropic ovarian failure
BMP15	XLD	300247	POF4, OD2	300510	Delayed puberty, primary/secondary amenorrhea, small ovaries, follicles absent, hypoplastic uterus, hirsutism, absent pubic/axillary hair
FLJ22792	XLR	300603	POF2B	300604	Weak teeth, delayed puberty, primary amenorrhea, osteoporosis
DIAPH2	XLD	300108	POF2A	300511	Secondary amenorrhea
FSHR	AR	136435	OD1	233300	Osteoporosis, primary amenorrhea
MCM9	AR	610098	OD4	616185	Short stature, low weight, underdeveloped breasts, no ovaries, retarded bone age and development of pubic/axillary hair, primary amenorrhea
SOHLH1	AR	610224	OD5	617690	Short stature, absent thelarche, primary amenorrhea, hypoplastic/no ovaries, small uterus, retarded bone age
PSMC3IP	AR	608665	OD3	614324	Underdeveloped breasts and absent pubic hair, hypoplastic uterus, primary amenorrhea
AMH	AD	600957	POF	/	Primary/secondary amenorrhea
AMHR2	AD	600956	POF	/	Primary ovarian insufficiency
DAZL	AR	601486	POF	/	Low ovarian reserves
GDF9	AR	601918	POF14	618014	Primary amenorrhea, no breast development, delayed pubic hair development
LHCGR	AR	152790	POF	/	Primary amenorrhea
INHA	AD, AR	147380	POF	/	Primary amenorrhea
PGRMC1	AD	300435	POF	/	Hypergonadotropic hypogonadism, amenorrhea
POU5F1	AD	164177	POF	/	Small ovaries without follicles
TGFBR3	AD	600742	POF	/	Premature ovarian failure

(continued on next page)

Table S1 *(continued).* Genes associated with male and female infertility (https://www.omim.org/)

WT1	AD	607102	POF	/	Secondary amenorrhea
SGO2	AR	612425	POF	/	Ovarian insufficiency
SPIDR	AR	615384	POF	/	Hypoplastic/no ovaries
EIF4ENIF1	AD	607445	POF	/	Secondary amenorrhea
NUP107	AR	607617	OD6	618078	No ovaries, small uterus, no spontaneous puberty
NANOS3	AD	608229	POF	/	Primary amenorrhea
ZP3	AD	182889	OOMD3	617712	Oocyte degeneration, absence of zona pellucida
TUBB8	AD, AR	616768	OOMD2	616780	Oocyte arrest at metaphase I or II; abnormal spindle
ZP1	AR	195000	OOMD1	615774	Absence of zona pellucida
PATL2	AR	614661	OOMD4	617743	Oocyte maturation arrest in germinal vesicle stage, metaphase I or polar body 1 stage; abnormal polar body 1; early embryonic arrest
ZP2	AR	182888	OOMD6	618353	Abnormal of zona pellucida
TLE6	AR	612399	PREMBL1	616814	Failure of zygote formation
PADI6	AR	610363	PREMBL2	617234	Recurrent early embryonic arrest
SYCP3	AD	604759	RPRGL4	270960	Fetal loss after 6-10 weeks of gestation
F2	AD	176930	RPRGL2	614390	Recurrent miscarriage
ANXA5	AD	131230	RPRGL3	614391	
NLRP7	AR	609661	HYDM1	231090	Gestational trophoblastic disease
KHDC3L	AR	611687	HYDM2	614293	
			Male infertility		
Gene	**Inheritance**	**OMIM gene**	**OMIM phenotype**	**OMIM phenotype ID**	**Sperm defect**
NR5A1	AR	184757	SPGF8	613957	AZS/OZS
SYCP3	AD	604759	SPGF4	270960	AZS/OZS
ZMYND15	AR	614312	SPGF14	615842	AZS/OZS
TAF4B	AR	601689	SPGF13	615841	AZS/OZS
TEX11	XLR	300311	SPGFX2	309120	AZS
NANOS1	AD	608226	SPGF12	615413	AZS/OZS/OZS+ASTHZ+TZS
PLK4	AD	605031	/	/	AZS
MEIOB	AR	617670	SPGF22	617706	AZS
SYCE1	AR	611486	SPGF15	616950	AZS
USP9Y	YL	400005	SPGFY2	400042	AZS
SOHLH1	AD	610224	SPGF32	618115	AZS
TEX15	AR	605795	SPGF25	617960	AZS/OZS
HSF2	AD	140581	/	/	AZS
KLHL10	AD	608778	SPGF11	615081	OZS; TZS; AZS
AURKC	AR	603495	SPGF5	243060	TZS (macrozoospermia)
DPY19L2	AR	613893	SPGF9	613958	TZS (globozoospermia)
SPATA16	AR	609856	SPGF6	102530	TZS (globozoospermia)
PICK1	AR	605926	/	/	TZS (globozoospermia)
BRDT	AR	602144	SPGF21	617644	ASS
SUN5	AR	613942	SPGF16	617187	ASS

(continued on next page)

Table S1 *(continued).* Genes associated with male and female infertility (https://www.omim.org/)

SLC26A8	AD	608480	SPGF3	606766	AZS
CATSPER1	AR	606389	SPGF7	612997	AZS
SEPT12	AD	611562	SPGF10	614822	AZS; OZS+ASTHZ+TZS
CFAP43	AR	617558	SPGF19	617592	MMAF
CFAP44	AR	617559	SPGF20	617593	MMAF
DNAH1	AR	603332	SPGF18	617576	MMAF
PLCZ1	AR	608075	SPGF17	617214	OAF

SPGF = spermatogenic failure; OZS = oligozoospermia; AZS = azoospermia; ASTHZ = asthenozoospermia; TZS = teratozoospermia; OZS+ASTHZ+TZS = oligoasthenoteratozoospermia; ASS = acephalic spermatozoa syndrome; MMAF = multiple morphological abnormalities of the flagellum; OAF = oocyte activation failure; AR = autosomal recessive; AD = autosomal dominant; XLR = X-linked recessive; YL = Y-linked; OD=ovarian dysgenesis; POF = primary ovarian failure; OOMD=oocyte maturation defect; PREMBL=preimplantation embryonic lethality; RPRGL=recurrent pregnancy loss; PREMBL=preimplantation embryonic lethality.