Women over 50 years of age routinely conceive and deliver following the transfer of embryos originating from donor oocytes, and even cases of successful pregnancies in women over 60 years have been reported in the peer reviewed literature and headline news [1–4]. Advances in our understanding of the early human embryonic biology, and the ability to routinely obtain oocytes from young donors, have enabled the transfer and successful implantation of embryos into the uterus of peri- and postmenopausal women [5,6]. As a consequence, women even beyond their assisted reproduction fecundity, up to the sixth decade of life, are now able to conceive, carry pregnancies and deliver. There is a growing trend in affluent societies to delay childbearing, so the number of women seeking and achieving pregnancies in advanced ages is constantly rising. The advanced maternal age, beyond the limit of natural fecundity, is associated with substantially more maternal and fetal complications [7,8]. Despite the age difference, oocyte donation in elderly women is as successful as IVF in the donors’ age group. The uterus retains its receptivity to embryo implantation for a substantial period of time after the ovarian function decays, as long as sufficient exogenous hormonal support is provided. The implantation rate of embryos from donated oocytes is almost unaffected by age [7], but the chance for a successful final outcome certainly is.

Pregnancies at menopausal age raise major medical and ethical concerns regarding the well-being of both mother and child. Another issue is determining the society’s position regarding facilitating women of advanced age to reproduce way beyond natural limits. If such choices are acceptable, at which financial, social and personal risk should this be pursued? It is the objective of this review to raise the medical and ethical questions and to try to answer some of them from our point of view.

Medical aspects & considerations
Several considerations are important when planning the possibility of pregnancy in menopausal women.

Fertility, fecundity & abortions
Fertility and fecundity decrease as a woman’s age advances [9]. The declining quality of the oocyte is the leading cause of age-related decline in fecundity. The endometrial receptivity and the chance of implantation also decrease with age [10], but this can be readily corrected by hormonal preparation [5]. Other factors such as the male partner, coital frequency, endometriosis and tubal pathologies may also coexist. The fecundity and cumulative pregnancy rates in women over the age of 35 years is decreased. In addition, the miscarriage rate increases in parallel with maternal age, up to 20–40% in perimenopausal women, mainly due to an increase in chromosomal aberrations [11]. Most of these are readily corrected when oocytes from young donors replace the aging oocytes and adequate endometrial preparation with exogenous estrogens and progestagens is provided.

Pregnancy-associated physiological changes
Pregnancy induces hemodynamic, respiratory, renal and endocrinologic changes that are a considerable stress even on young women. Cardiac output is increased by 40% by the beginning of the third trimester, and increases even more...
during labor. The respiratory volumes and effort, and the glomerular filtration rate are also significantly increased [12]. The prevalence of hypertension, heart diseases, chronic lung disease, renal disease and diabetes is age dependent [13], as well as the mortality associated with neoplasms and heart diseases [2]. Gestational trophoblastic diseases, myomatous uteri and urinary tract infections are more prevalent among older women, possibly complicating pregnancies in this age group [14–16]. Thus, pregnancy in the older population potentially constitutes a major maternal health risk. Heart diseases, diabetes, hypertension and placental complications are associated with maternal age [13,17]. Dynamic tests designed to unmask occult diseases such as ergometry, thallium scans and spirometry do not reliably mimic the changes anticipated in advanced pregnancy. No diagnostic test actually and faithfully simulates the conditions of pregnancy. Therefore, the negative predictive value of normal functional heart or lung tests performed before pregnancy is uncertain. For example, it is unclear if a pregestational negative thallium dipiridamole scan does predict a pregnancy free from cardiac complications.

**Obstetrical & intrapartum complications**

Advanced maternal age is a prominent risk factor of chronic essential hypertension, as well as pregnancy-induced or -exacerbated hypertensive complications such as pre-eclampsia. Impaired glucose tolerance is an age-related phenomenon. Therefore, it is not surprising that gestational diabetes is more prevalent as the maternal age increases. These two complications were reported to be of high prevalence in the advanced age group in almost all the published reports on this issue. Moreover, in studies in which the advanced age group was stratified into subgroups, the prevalence of these complications paralleled aging [18]. Salihu *et al.* had investigated the rate of complications in two groups of pregnant women in the USA: ages 40–49 and over 50 years were evaluated. The occurrence rates of cardiac diseases (8.8 vs 24.1%), hypertension (23.6 vs 27.8%), diabetes (61.9 vs 72/4%), and pre-eclampsia (45.1 vs 85.3%) were all high, and increased in the older age group [13]. Additional studies showed similar results [7,8,18]. The frequencies of hypertensive complications and diabetes in pregnancy were extremely high among pregnant women of advanced age. Women aged 50 years and older were more likely to be hospitalized during pregnancy (63%) than women younger than 50 years of age. Age was found to independently correlate with the occurrence of placental abruption and placenta previa, even after controlling for confounding factors such as smoking or hypertension [15]. After age stratification, the prevalence of these two complications was found to be in direct correlation with maternal age, even within the oocyte donation recipient group. The older the patient, the more likely she is to have placenta previa, placental abruption or both [18]. Subtle, otherwise unnoticed, changes in the uterine vasculature might be the independent age-related risk factor responsible for this observation. All these risks were markedly increased in the case of multifetal gestations [7], which is not uncommon in the assisted reproduction technologies setup. Therefore, women of advanced age are more likely to experience preterm labor and deliver prematurely [2,7,8,13,18,19]. The prevalence of low birth weight and preterm deliveries was found to be significantly increased in those over the age of 50 years for both singleton and multiple pregnancies [7].

The incidence of different labor patterns and instrumental deliveries in older primiparas differs between published reports even after controlling for confounding factors [20,21]. Primiparity, prior infertility and oocyte donation were found to be strongly associated with the performance of cesarean sections over a decade ago [19]. Presently, almost all women older than 50 years are delivered by cesarean section, even in the absence of complications. The obstetrical implications of this are mainly in the short term. Although longer hospitalization periods and increased febrile morbidity were reported, intensive care hospitalization and blood transfusion rates were not [18]. Since most of these women will not deliver again, more serious complications in future pregnancies such as scar implantation are unlikely. Although maternal morbidity was increased in the older women, the overall neonatal outcome did not appear to be affected [19,21].

**Maternal mortality**

Direct and indirect maternal mortality increases in correlation with age, mainly due to pre-existing conditions exacerbated by pregnancy-associated complications such as toxemia, placental abruption, postpartum hemorrhage and thromboembolic phenomena [12]. The tendency to use cesarean section in almost all women who conceive over 50 years does not appear to contribute to maternal mortality [2]. Sporadic maternal deaths following ovum donation in advanced age
have been published [22], but most cases are not reported in order to avoid legal complications.

**Neonatal outcome**

An increased rate of low birth weights, preterm deliveries, small for gestational age infants and perinatal mortality was reported in neonates of mothers of advanced age [2,13,19,23]. On the other hand, the rate of low Apgar scores, asphyxia and metabolic complications was not increased in this group [18,19]. All these probably result from the obstetric complications prevalent in this age group, which result in preterm deliveries. An increased prevalence of congenital anomalies in the offspring of older premenopausal women conceiving from their own oocytes has been reported, attributed mainly to the older gamete age. This is of no concern if oocytes from young donors are used. The long-term psychological and social effects of being the child to elderly parents are controversial and vary greatly between populations and societies.

**Oocyte donation programs**

The currently acceptable indications to use donor instead of own oocytes are physiological and premature ovarian failure, low ovarian response to exogenous gonadotropins, and carrihership of disorders inherited through mitochondrial DNA. The oocytes are obtained either from women undergoing IVF who donate excess oocytes or paid designated volunteers. Fresh embryo transfer is performed into a synchronized prepared uterus. Alternatively, the embryos can be cryopreserved and transferred in another cycle. Cryopreservation is feasible by vitrification (oocytes and embryos) or slow freezing (embryos only) [24]. In the case of menopausal women, artificial endometrial preparation is accomplished using estrogen and progesterone supplements [5]. After pregnancy is established, both estrogen and progesterone administration continues until placentation occurs. If regular ovulations still occur despite the advanced age, and the ovarian steroid hormone secretion is maintained, embryo transfers based on spontaneous cycles without artificial endometrial preparation are also a feasible option. The reported global pregnancy rate is currently 50% per transfer cycle in most programs.

The possibility to cryopreserve embryos and oocytes has decreased the willingness of women and couples undergoing IVF treatments to donate oocytes, since most prefer to freeze them for future use [25]. Therefore, in most programs, the oocytes are obtained from designated volunteers who are paid for their ‘donation’. Candidate donors must be healthy, under 35 years of age, and screened negative for sexually transmitted diseases and hereditary disorders. They must be free of any current or past significant medical problem. The maintenance of anonymity is important for the sake of the donor, the recipient and the offspring. The donors undergo moderate induction of ovulation and oocyte recruitment procedures under ultrasonographic guidance. Excessive ovarian stimulation is hazardous to the donor and is also detrimental to the quality of the obtained oocytes. A treatment protocol using a gonadotropin-releasing hormone analog instead of human chorionic gonadotrophin to trigger oocyte maturation protects the donor without reducing the chance of implantation in the endometrium of the separately prepared recipient [26].

In countries in which oocyte donations are performed, generally relevant legislation or directives exist, usually as a part of the regulations of the various aspects of human reproduction. In most cases, such regulations apply mainly to the donor, to protect her health, rights and anonymity [27]. Presently, ovarian stimulation and oocyte pick-up bears little risk to the donors. Oocyte donation to peri- and postmenopausal women is currently practiced in many centers worldwide. Women in perimenopause and beyond are the major patient group in need of oocyte donations. However, it is surprising that there is an international paucity of regulations that apply to the recipients, despite the significant hazards that pregnancy might impose on them. A large proportion of oocyte donations treatments are performed in a reproductive tourism setup, with no actual supervision on age and health status at the recipients’ end.

**Ethical aspects**

The success rate of oocyte donation is almost unaffected by age. Any woman with an intact uterus and reasonable health is a potential candidate. This raises the discussion whether an age limit should be imposed when applying this reproductive technology. Limiting the reproductive choice should be seriously considered, taking into account the welfare of the mother, offspring, family and society, as well as the right for privacy and personal freedom in making reproductive choices. It is for each society to determine its position towards enabling elderly women to become pregnant using advanced technology. In addition, a priority system for the allocation of the scarce donated oocytes should also be established, reflecting the local values and laws.
Issues of choice
The will to reproduce is strong in most human societies. The modern and liberal ones respect and elevate the individual's rights to privacy and autonomous reproductive choices. New reproductive options are possible due to the availability of assisted reproductive technologies. Oocyte donation to an older woman is such a reproductive choice. In an era of increased life expectancy and enhanced life quality, a menopausal woman may not feel unsuitable to deliver and raise a child. In developed countries, a woman who has reached the age of 50 years in good health has an average additional life expectancy of more than 20 years, long enough to raise a child to adulthood. Many women decide to postpone childbearing until certain career and financial achievements have been obtained. This point might parallel menopause quite easily. Infertile young couples divert a tremendous amount of personal energy and resources in order to achieve conception. Childbearing in younger women with life-threatening medical conditions or with inherited disorders is not prohibited in open societies. In some countries these efforts are substantially supported through the public health system. Refusing the presently feasible option of oocyte donation to women of advanced age, for this reason solely, constitutes a denial of her reproductive choice, and might be considered even a type of age-based discrimination. In addition, society does not view men and women equally when it comes to age. Older women are considered unable to naturally have children, whereas older men are considered suitable for parenting in later life. This cannot be regarded as discriminatory, since women bear children, deliver them, nurse them and bear the medical risks of pregnancy. Safely extending the age of biological motherhood by a few years is an opportunity to modestly correct this long-standing gender-based difference.

However, it can be argued that enabling pregnancy at an age in which it is impossible to conceive naturally might be hazardous, and is an action against our biological limitations. On the other hand, this argument can be extended to other ‘unnatural’ situations resolved by assisted reproduction. Currently, it seems totally unacceptable to deny young couples childbearing with severe male factor infertility, absent fallopian tubes, premature ovarian failure or anovulation on the grounds that conception should happen ‘naturally’. It is axiomatic that assisted reproductive technologies should be made available exactly in these cases. Then why should women be denied conception on the grounds of age alone? Recent societal changes emphasize women’s career achievements, equal contribution and opportunities. Many women decide to postpone childbearing as a consequence of these changes, but this is not always the case when a woman or couple seek oocyte donation. Some women find themselves in a new marriage desirous of a child with their new partner. Others lose their children to disease, accidents or violence, and would like to deliver again. In other cases, infertile women who at the relevant point in time could not be assisted by the available technology have reached menopause. Denying access to oocyte donation in such circumstances, on the grounds of age alone, may appear cruel and unfair.

Welfare of the child
Opponents to pregnancies in women of advanced age may base their arguments on the interest and welfare of the potential child, implying that older individuals are less capable of coping with the physical and psychological stress of parenting. Having parents of advanced age may cause children to endure a greater generation gap, lack grandparents or lose their parents at a relatively young age. On the other hand, older parents, singles and couples, are more mature and experienced. Generally, they enjoy more free time and a better financial status than younger couples engaged in the race of life. In the case of prolonged infertility, the long-lasting desire for a child might be more beneficial than detrimental. Considering all these arguments, it is reasonable to assume that, unless a significant parental physical or mental impairment exists, the welfare of children born to mothers or parents of advanced age is not adversely affected. Nevertheless, providing a supporting social backup system of involved relatives in case of parental impairment or death is a wise, although not mandatory, step. A crucial additional factor to the psychological well-being of the offspring is maintaining the donor anonymity, although the policy towards possible disclosure after adulthood should be considered and publicly discussed.

Coping with the medical risks
‘Primum non nocere’ is a universal medical concept. It is also accepted among all healthcare providers that a woman’s well-being is more important than any reproductive choice or plan. The high prevalence of complications is attributed mainly to the increased risk of chronic diseases and conditions in the population of older women. However, most of the data published
Donation of gametes, either sperm or oocytes, is not practiced in several European countries, South America and Islamic countries, because of religious reasons. According to Judaism, oocyte donation is permissible only if the donor is not a married woman. The three main branches of Christianity prohibit oocyte donation: the Roman Catholic, the Eastern Orthodox and the Protestant churches. Oocyte donation is not permissible by Islam and parallels adultery. Hinduism and Buddhism do not ban donation of oocytes.

Oocytes for donation are scarce, and the issue of their allocation is an ethical dilemma. Unfortunately, allocation is often based on ability to pay rather than the urgency and strength of need. Although often unpractical, an ideal society should aspire that women and couples who have been deprived of children are given first priority. It is also ethically acceptable to give priority to young women with premature ovarian failure or ovarian dysgenesis, rather than to menopausal woman with or without children. Ideally, oocyte donation should be voluntary and altruistic, but this expectation is unrealistic in our society. However, other forms of donor compensation should be considered and encouraged instead of direct payment.

Any restrictions on providing donor oocytes to women of advanced age must be based on sound objective medical, psychological or social grounds. Reproduction is a basic right in our society. However, other forms of donor compensation should be considered and encouraged instead of direct payment. Some suggest that this limit should be a deduction of 20 years from the average life expectancy (i.e., ~60 years of age). The public discussion in the media regarding reproduction at this age is harsh. Those who provide oocyte donation in this age group are accused of tampering with nature, acting irresponsibly or playing God. On the other hand, the opponents are accused of being paternalistic and arrogant. The public opinion in most western countries, where late motherhood using donor oocytes is feasible, is often split. The questions of where to draw the line and who should decide are not easily resolved.
It is our belief that the recipient age limit is not only a medical issue, but also has a serious social and ethical significance. As such, the maternal age limit to pregnancy beyond natural fecundity should be determined locally in every society or political entity, jointly by physicians, specialists in social sciences, public leaders, politicians and bioethics experts. The factors to be considered in such a discussion should include local life expectancy, the well-being of the population, the quality, availability and cost of the various necessary medical services, the possibility to pursue fertility treatments, the social support available to parents of advanced age, and the significance of childbearing in the local culture. For example, in the most recent Israeli legislation (2010), the maximal age for a recipient of embryos originating from donated oocytes was determined to be 54 years [28]. This limit was established after years of public discussions preceding the preparation of the law regulating oocyte donation from designated donors. This age limit is the product of a process that reflects the long Israeli life expectancy, the high level and low cost of the medical system, and the great importance of childbearing in most of the communities comprising the Israeli society. This process can result in a different age limit elsewhere.

Conclusion
Presently, it is becoming more common and socially acceptable for peri- and postmenopausal women to bear children. Advances in our understanding of human reproduction and the possibility to obtain oocytes safely from young donors have made pregnancies in older women feasible. The impact of advanced age on the maternal well-being and outcome of the pregnancy remains controversial. Pregnancy beyond the natural fecundity could constitute a major maternal and fetal health risk. On the other hand, with appropriate preconception screening and meticulous antepartum and intrapartum surveillance, a reasonably successful pregnancy outcome can be expected in most cases, despite the higher prevalence of certain pregnancy-associated complications. Patients should undergo a proper medical and psychological evaluation before contemplating pregnancy at an advanced age in order to exclude those who will not be able to cope physically or psychologically.

The success of oocyte donation is almost unaffected by age, and any woman with an intact uterus is a potential candidate. This raises the question of introducing an age limit, preferably based on solid medical and social grounds. Denying the currently biologically feasible right to reproduce at an advanced age negates freedom and harms women’s reproductive choices.

It is essential that transparent guidelines are established so that pregnancy can be achieved safely and result in a healthy mother and child. Although pretreatment health screening is effective, it is our belief that an age limit should be applied. The precise determination of this age limit should be set, taking into consideration local social and medical factors such as culture, religion, life expectancy, quality of medical care and antenatal management.

Future perspective
Social, medical and technological changes during the last 30 years of assisted reproduction enable the safe retrieval of oocytes from young donors in order to achieve pregnancies in peri- and postmenopausal recipients. Although pregnancy beyond the natural fecundity does harbor substantial maternal fetal and neonatal risks, those can be minimized if proper screening is employed and anticipatory antenatal care is provided. We believe that any decision to limit the recipients’ age should be specific to the local social and medical circumstances in

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<td>• The human fecundity declines with aging primarily due to a decrease in the quality of the ova.</td>
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<td>• Pregancies can be achieved beyond the age of fecundity by using oocytes safely retrieved from young donors.</td>
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<td>• The predictive value of conventional screening tests performed prior to such pregnancies is uncertain.</td>
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<td>• Oocyte donation pregnancies at advanced age are associated with an increased prevalence of maternal and fetal complications, but most of them result in a favorable outcome if meticulously prepared and looked after.</td>
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<td>• Parenthood at advanced age raises a conflict between the right to autonomy in reproductive choices and the potential welfare of the offspring.</td>
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<td>• Setting an age limit to pregnancy (via oocyte donation) by legislation is warranted and should take into consideration local and timely social and medical individual and public factors. This limit should be periodically re-evaluated.</td>
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a given time. Such limits should be periodically re-evaluated, taking into consideration advancements in medicine, public health and reproductive science. The current presently acceptable age limitations (~50 years of age) were considered adventurous 20 years ago. We foresee that if (and when) the life expectancy and life quality parameters continue to rise in the future, the accepted age limit to pregnancy via oocyte donation will also rise.

Financial & competing interests disclosure
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No writing assistance was utilized in the production of this manuscript.

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• of interest
• The report of the first pregnancies from oocyte donation.
• Describes the more recent results of pregnancies at advanced age in a
developed country with an accessible, high-quality public health system.
• Describes the actual more recent results of pregnancies at advanced age in a
developed country with an accessible, high-quality public health system.