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REVIEW

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Early pregnancy loss in IVF: a literature review

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Abstract

Human reproduction is an imperfect process despite years of evolution. It is estimated that only 30% of conceived pregnancies end up with a live birth (Hum Reprod Update 8:333-343, 2002). Although the IVF cycle clinical pregnancy rate is estimated to be above 60%, the actual live birth rate is still well below 50% (Reprod Biomed Online 40:201-206, 2004). Errors of implantation, embryonic genetic mutations, structural as well as chromosomal abnormalities, endometrial aberrances as well as abnormal sites of implantation are all conditions that could be associated with a positive pregnancy test yet a non-viable pregnancy outcome. In this extensive literature review, we detailed the different risk factors hindering a successful reproductive outcome post-IVF in terms of early pregnancy loss. We also reviewed the different treatment modalities available to improve the prognosis of such patients.

Keywords Chorionic gonadotropin, Pregnancy, Blighted ovum, Reproductive techniques, Assisted abortion, Spontaneous

Background

Pregnancy is characterized by the presence of beta human chorionic gonadotropin (hCG) in the maternal blood. The clinical significance of this positive blood test is related to the sonographic translation of an intra-uterine viable gestational sac (GS). HCG production starts by the placental syncytiotrophoblasts as early as the pre-implantation phase of embryonic development [1]. The quantitative detection of serum hCG however coincides with the embryonic implantation phase, 7–8 days post-ovulation and fertilization in natural conception cycles and 3–4 days post-embryo transfer in IVF cycles [2]. Despite that IVF cycle clinical pregnancy rate is estimated to be above 60%, the actual live birth rate is still well below 50% [3]. Errors of implantation, embryonic genetic abnormalities, endometrial aberrances as well as abnormal sites of implantation are all conditions that could be associated with a positive pregnancy test yet a non-viable pregnancy outcome. Ectopic pregnancy, biochemical pregnancy (BCP), anembryonic pregnancy (AP), and clinical spontaneous abortions (SAB) are examples of pregnancies resulting from the errors and aberrations mentioned. BCP, AP, and SAB will be referred to as early pregnancy loss (EPL) and will be the topic of our review.

We performed an extensive narrative literature review to pinpoint the real incidence of EPL in the setting of IVF as well as the risk factors predisposing to the failure of the take-home-baby IVF concept. Different treatment modalities were reviewed to provide the infertile couple suffering from an EPL event with the proper counseling and treatment plan to avoid similar negative outcomes in future treatment cycles.

Definitions

BCP, chemical, trophoblast in regression, preclinical pregnancies, or non-visualized pregnancy losses are

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pregnancies diagnosed with a transient rise of hCG [4]. The BhCG usually increases above 5 mIU/ml to a maximum value of 100 mIU/ml and then drops to be followed by vaginal bleeding before any sonographic documentation of an intra-uterine GS [5]. According to Sung et al, the cut-off value for BCP on day 12 post-ovum pickup in fresh embryo transfer (ET) (day 7 post-ET) was 20 mIU/ml which was significantly less than that for the live birth patients (65.2 mIU/ml). In frozen ET, the cut-off for biochemical pregnancies was 29 mIU/ml while for the live birth it was 73 mIU/ml [6]. It should be noted that according to the American Society of Reproductive Medicine (ASRM), a BCP is not considered a clinical pregnancy, and thus patients suffering from recurrent BCPs are not diagnosed as patients having RPL [7].

SAB or a clinical spontaneous abortion is a pregnancy that is detected on the uterine sonographic evaluation but is lost due to the arrest of embryonic development prior to the second trimester or 12 weeks of gestation. AE or blighted ovum on the other hand results from embryos succeeding in their implantation without any signs of embryonic development. Theoretically speaking, AP can be considered as a subset of SAB [8].

Incidence

An important factor in determining the incidence of BCP is the day serum hCG was tested. It is well known that hCG production starts in the pre-implantation phase and serum detection can be possible as early as 1–2 days post-implantation [2]. In the fertile population, it was found that the BCP rate ranged between 13 and 22% [9]. These values were based on data published more than 20 years ago, and the detection of BCP was founded on the detection of urine hCG after the delay of the menstrual period. It was postulated that the majority of BCP in the general population goes unnoticed before the period is delayed [7]. Hence, the day of the blood test should be chosen with care to avoid false positive findings, add to that, serial blood hCG levels should be considered whenever there is a suspicion of an abnormal initial value or slow rise in hCG [10].

Age is a major contributing factor to EPL in the setting of non-tested embryos. While BCP incidence was not affected by age, SAB rates increased proportionally with age. In the setting of the transfer of non-tested embryos, the SAB rate increased from 10.6% in patients younger than 35 years to 33.7% in patients older than 40 years old [3]. AE which are included in the SAB category account for almost half of the clinical pregnancy losses [11]. In the context of euploid embryos, BCP incidence ranged between 6.8% and 20% in NGS (Next Generation Sequencing) and aCGH (Array Comparative Genomic Hybridisation) euploid-tested embryos, respectively, while SAB rates were estimated to be around 12% in both groups [12]. Interestingly, the miscarriage rate of euploid embryos remained stable with advancing maternal age which is an important point when planning the treatment of an infertile couple [13, 14].

Day of ET was found to affect the incidence of BCP. Xiao et al. in 2019 found that day 3 ET was related to a 16.7% BCP rate in comparison to 9.5% in the blastocyst transfers [15]. These findings were supported by Wang et al in 2017 in which the authors noted that day 3 ET were more prone to errors in implantation [16]. Zeadna et al showed that BCP rates did not differ between fresh or frozen non-tested ET (13.8%) but were significantly less when compared to the fertile population (18%) [9]. Contrary to Zeadna et al.'s findings, Wang et al in 2017, revealed that blastocyst FET was associated with increased rates of BCP and SAB when compared to fresh blastocyst transfers (19.6% and 13.8% for BCP and 14.9% and 11% for SAB respectively) [16].

The rates of BCP and SAB in the different populations discussed are summarised in Table 1.

Causes and risk factors

Oocyte/embryo-related factors

There's a growing body of evidence suggesting that the quality of the oocyte is important for proper embryogenesis. It is postulated that oocyte dysmorphism could be related to developmental errors and chromosomal abnormalities [18]. For example, embryos resulting from oocytes showing clustering of smooth endoplasmic reticulum (sER) were found to have an extremely low pregnancy rate and a higher BCP rate of 22% in comparison to 3.5% in the case of embryos deriving from normal oocytes [18]. A possible explanation is that oocyte dysmorphism might hinder proper division post-fertilization due to errors in the meiotic spindle giving rise to either chaotic mosaicism with subsequent mitochondrial

Table 1 Incidence of BCP and SAB in different populations

Population	Incidence of BCP	Incidence of SAB
Fertile general population/ spontaneous conception	13–22%[*]	50–60%[#]
Fresh ET (non-tested)	13.8%[*]	10.6–33.7%[α], age dependant
FET (non-tested)	13.8–19.6%[*, β]	10.6–33.7%[α], age dependant
Day 3 ET	16.7%[β]	13.7%[δ]
Day 5 ET	9.5% [β]	11%[δ]
aGCH tested embryos	20%[ξ]	12% [ξ]
NGS-tested embryos (age-independent)	6.8% [ξ]	12%[ξ]

References: [*][10], [#][17], [α][3], [β][15], [ξ][16], [δ][14]

damage or errors in mitotic divisions producing mosaic embryos. This mitochondrial damage might lead to poor energy production which is vital for the dividing and implanting embryo. Shortage in energy levels might lead to BCP as the embryos fail to proceed with the implantation process.

It is suspected that BCP could also result from embryos suffering from genetic abnormalities that lead to embryo wastage at the early stages of implantation. These genetic aberrations or de novo mutations can affect the ability of the embryo to survive which explains the persistence of BCP even after euploid embryo transfers [17, 19].

According to Bu et al in 2020, advanced maternal age, RPL, poor ovarian reserve, and a history of a low number of oocytes at retrieval were associated with significantly increased SAB rates [3]. Dahan et al. in 2020 also found that maternal age did not affect the incidence of BCP (9.8–13.6%) contrary to SAB rates which increased significantly with age reaching 50% above the age of 40 highlighting the deleterious effect of aging oocytes associated dysmorphism as well as the increased incidence of age-related chromosomal aneuploidies [20, 21]. Concerning AP, Ouyang et al., in a comparison between embryonic and anembryonic miscarriages post-IVF, found that embryonic pregnancies were more commonly associated with chromosomal abnormalities than anembryonic pregnancies (54% versus 37.5% respectively). In anembryonic pregnancies, the incidence of chromosomal aberrations was more common when a yolk sac was seen than when an empty sac was detected (46% versus 29% respectively). Ouyang et al suggested that non-chromosomal related factors might have a direct impact on early embryonic development leading to its arrest at early stages and hence the absent fetal pole and the empty sacs. If the embryo manages to bypass those hurdles, then later causes of EPL including AP with yolk sacs would be more associated with chromosomal abnormalities [11]. The incidence of AP was higher in consanguineous couples when compared to non-consanguineous couples (68.5% versus 31.5%) [22]. As per Melado et al in a recent publication, consanguineous couples are at a higher risk of having embryos with segmental aneuploidies [23]. Keeping both findings in mind, the issue with genetic non-chromosomal abnormalities, non-detectable chromosomal abnormalities, and single gene disorders re-surface as probable causes of predisposition to the occurrence of AP rather than aneuploidy or structural chromosomal abnormalities per se as the only known causes. Embryos undergoing mitotic errors are known to contain at least 2 genetically different cell lines. These embryos are known as mosaic embryos [24]. Friedenthal et al showed that the exclusion of mosaic embryos from the transfer list led to the reduction of the incidence of BCP to as low as 6.8% [12]. Hence, one can postulate that mosaic embryos can be one of the causes of BCP as the mitotic errors that the embryos undergo decrease their implantation potential. SAB and AP on the other hand occur after implantation and the formation of the GS. Despite being at a lower rate in comparison to non-tested embryos, both BCP and SAB were still documented with the transfer of euploid embryos [25, 26]. This highlights the fact that miscarriages can also be attributed to factors other than aneuploidy. Thus, it is believed in the later setting, these miscarriages might be more related to hostile uterine factors or errors in the fetal formation post-implantation [12]. BCP and SAB from euploid embryos also shed light on the accuracy of the genetic testing, especially with the knowledge that the biopsied blastomeres originate from the trophectoderm solely. The inner cell mass is left untested and questions concerning the generalisation of the genetic testing result especially the euploid one on the embryo as a whole arise. Chuang et al found that up to 3% of tested embryos have euploid trophectoderm and aneuploid ICM [27].

Uterine factors

In 2019, Zanetti et al. published a retrospective study in which they highlighted that thin endometrium was a significant risk factor for BCP. This altered thickness might be related to a decreased endometrial receptivity hence hindering proper implantation necessary for a successful clinical pregnancy and later on a live birth. As per Zanetti et al. the cut-off limit for endometrial thickness was 11.1 mm for clinical pregnancy, 10.97 mm for SAB, 10.75 mm for no conception, and 9.74 mm for BCP [28]. Liu et al in 2018, analyzed around 40,000 ET cycles both fresh and frozen and they concluded that in fresh embryo transfers, pregnancy loss rates increased significantly from 22% to 30% when the endometrial lining measured at least 8 mm and when the lining was below 6 mm respectively. In FET cycles on the other hand, pregnancy loss rates increased to 47.8% when the thickness of the endometrium was below 6 mm in comparison to 26% when the thickness measured 8 mm and above, yet this difference was not found to be statistically significant. Those results also lacked statistical significance given that the proportion of embryo transfer cycles with an endometrium less than 7 mm was less than 5% of the whole population studied. Hence one can postulate that for fresh embryo transfers a cut-off limit of 8 mm is acceptable while for FET cycles 7 mm is the limit to be used in counselling especially from a clinical pregnancy and live birth rate perspective. In the same study, Liu et al. found that patients above 40 years old had significantly decreased chances of achieving the cut-off endometrium thickness [29].

In a retrospective study by Zhang et al. in 2021, ovulation induction FET cycles were found to have significantly lower miscarriage rates when compared to the HRT cycles (14.3% versus 21.7%) [30]. In another retrospective study by Godiwala et al in 2022, the superiority of natural cycles in decreasing the EPL rates when compared to HRT cycles was documented especially in ovulatory patients and in PCOS patients based on low-quality yet promising evidence in the metanalysis performed by Zhang et al. in 2022 [31, 32]. A possible explanation for the discrepancies between the endometrial preparation protocols might be attributed to the presence of the corpus luteum in natural or ovulation induction cycles. Others suggested that the increased endometrial thickness in response to letrozole use in ovulation induction cycles provided better support for implantation and ongoing pregnancies [33]. Devine et al. performed an RCT comparing different routes of luteal phase support. The group concluded that suboptimal progesterone supplementation in medicated cycles via vaginal route with lower doses of progesterone increased the rate of BCP and SAB [34]. The day of embryo transfer in relation to the age of the embryo being transferred was also investigated. As per Roelens et al., the retrospective study concluded that day 6 blastocysts were at higher risk of SAB when transferred on the 6th day of progesterone supplementation as compared to the transfer on the 7th day of progesterone supplementation (50% versus 21.4% respectively) [35]. Progesterone levels measured in medicated FET cycles prior to ET despite affecting pregnancy rates, were not found to significantly affect EPL rates [36, 37].

Endometrial anomalies, uterine malformations, as well as a history of endometriosis were also found to be significant factors in augmenting SAB rates [3, 38, 39]. SAB rates were found to be not affected at 10% in both the polyp and the non-polyp groups. This suggested that miscarriages of the already implanted embryos in the altered endometrium would be related to aneuploidies or other major uterine anomalies other than benign endometrial polyps [40]. Qui et al found that uterine malformations did increase miscarriage; however, the values reached statistical significance only in patients with septate uteri (23 versus 13%) in comparison to controls [39]. In the setting of endometriosis; however, the findings are contradictory. Yang et al. compared miscarriage rates in fresh ET between patients diagnosed with endometriosis and controls. The group concluded that endometriosis does not increase the miscarriage rate even in the presence of large endometriomas [41]. Multiple studies, however, support the negative impact of adenomyosis on reproductive outcomes with SAB reaching 31.9% [42]. It was noted by Bourdon et al in 2022 that the coexistence of endometriosis and adenomyosis increases the SAB rates significantly when compared to cases having only adenomyosis with an OR of 3.2 [43].

Implantation-related factors

Embryonic implantation is a very complicated process that necessitates synchronization of maternal and embryonic processes to ensure appropriate receptivity [44]. It is believed that implantation is governed by maternal checkpoints to limit the ability of unhealthy abnormal embryos to implant. This might explain the high incidence of BCP in the general population [19]. To have a successful pregnancy outcome, euploid embryos should bypass all the implantation checkpoints. It is believed that embryos communicate with the surrounding decidual cells via paracrine signals. It is via those signals that the endometrium distinguishes good from bad-quality embryos. In the case of good-quality embryos, the signals induce proper expression of pro-implantation factors and metabolic genes. However, when mediocre quality embryos (aneuploid, genetic abnormalities, poor morphology) attempt to implant, the migratory decidual cells prevent proper encapsulation within the endometrium based on the signals that they receive. This crucial checkpoint plays a pivotal role in preventing low-quality embryos from implanting. However, when an aneuploid embryo passes unnoticed or when a euploid embryo is perceived as a low-quality embryo, a miscarriage happens in most cases. The exact mechanism of this communication is unknown so far, yet it is postulated that hsa-miR-320a and hyaluronidase 2 are two signaling molecules that convey information to the migratory decidual cells and uNK cells about the well-being of the embryos [19, 45–47]. In case the implantation checkpoint is bypassed successfully, miscarriage can still happen, especially if defective decidual development and endovascular trophoblast invasion ensue.

Sperm-related factors

Zanetti et al. found that altered semen parameters were associated with increased BCP rates. The group found that in fresh cycles ending with BCP, male factor was the most common cause of infertility, accounting for roughly 1/3 of the cases. Further analysis revealed that in BCP cycles, a decreased total motile count by more than half, as well as a decreased sperm count by half, was considered significant. In cycles ending with SAB, mixed male and female factor was found to be the most common cause in 23.5% of the cases [28]. Thus, even if the embryo succeeds in reaching the blastula stage and is suitable for transfer, the effect of the abnormal paternal semen analysis should still be taken into consideration since multiple reports have noted the negative impact of semen abnormalities on early embryogenesis, as well

as the implantation potential of the embryo. This can be explained partly by the preponderance of chromosomal or genetic abnormalities that can be unveiled during embryogenesis, as well as the decreased implantation potential of chromosomally normal embryos [28, 48].

The sperm DNA fragmentation index (DFI) has also been extensively studied. A systematic review and meta-analysis performed in 2008 showed that sperm DNA fragmentation is associated with increased rates of miscarriages post-IVF treatments [49]. However, in a 2015 meta-analysis, it was found that elevated DFI was not significantly associated with either BCP or SAB rates [50]. Haddock et al. compared the sperm DNA fragmentation of fertile males and males with a history of miscarriages of either spontaneous conception or ART-conceived pregnancies. The study concluded that couples suffering from miscarriages had a higher DNA fragmentation index, with an average of 33% DNA sperm damage [51].

Immune factors

Pregnancy necessitates a certain level of immune suppression to protect the allogenic fetus from being rejected. The natural process of implantation involves the spreading of the fetal trophoblast within the maternal uterine niche to allow proper placentation. The main elements in charge of the immune system downregulation during pregnancy are the natural killer (NK) cells [52]. Three different populations of uterine NK cells have been recently described to be involved in the feto-maternal interphase regulation which is usually activated by the interconnection between the maternal uterine NK cells receptors, killer immunoglobulin-like receptors (KIRs) that are expressed on uNK1, and embryo's HLA-C ligands [53, 54]. Alecsandru et al. documented alterations to this maternal immunomodulation, especially in the inhibitory KIR AA genotype carriers, leading to excessive suppression of uNK cells predisposed to SAB [54, 55]. Brosens et al. and Lucas et al. postulated that when the uterine population of NK cells decreases, the ability to eliminate the aging decidual cells decreases, thus increasing the risk of endometrial tissue breakdown and pregnancy loss [19, 56].

Auto-immune connective tissue disorders are also associated with increased SAB rates due to errors in immunomodulation [57]. Auto-immune thyroiditis was found to increase SAB rates in women testing positive for thyroid antibodies [58, 59]. The ASRM suggests testing for thyroid antibodies when TSH values are above 2.5 mIU/L [58]. Safarian et al. found that the present data is controversial concerning the effect of auto-immune thyroiditis on the SAB rates, especially in patients undergoing ICSI. They concluded that ICSI might have a protective effect against EPL in infertile patients. A recent meta-analysis by Venables et al. revealed that thyroid auto-immunity had no impact on EPL rates of ART cycles in both euthyroid and sub-clinical hypothyroid patients [60]. The exact mechanism remains unknown; however, it is thought that the antibodies either cause immune dysregulations at the feto-maternal interface or predispose the patient to develop overt hypothyroidism [59].

Endocrine and lifestyle-related factors

Polycystic ovarian syndrome (PCOS) was found to significantly increase the SAB in both lean and obese patients [3, 61]. Luo et al. showed that PCOS per se in patients with normal BMI was associated with an increased risk of euploid SAB with an OR of 2.9 [62]. Multiple studies have shown that elevated body mass index (BMI) was associated with increased rates of miscarriages with an OR ranging between 1.2 and 1.9 irrespective of the method of conception. Tremellen et al. found that SAB rates of euploid embryos increased significantly with increasing BMI. The SAB rate in lean patients was 14.9% in comparison to 41.9% in obese patients with a BMI > 30 kg/m^2 [62]. The exact mechanism of the deleterious effect of obesity on fertility and pregnancy remains to be elucidated; however, most authors agree that it is multifactorial, especially given the association of obesity with other comorbidities. Of the suggested theories is the inadequate luteal phase support characterized by low progesterone levels, as suggested by Goh et al. [63]. The resultant abnormal decidualization might be the cause of increased SAB and reduced live birth rates. Another theory is that obesity is related to an altered inflammatory profile and increased oxidative stress. Alteration of endometrial haptoglobin levels and decreased progesterone levels, which are potent enhancers of anti-oxidant factors production and normalization of the inflammatory profile, have been described in obese patients [64–66]. EPL.

Table 2 summarizes the different risk factors and the possible mechanisms leading to EPL.

Treatment suggestions

Regarding EPL, it is already known that chromosomal abnormalities are the culprit in more than half of the cases [71]. In patients above the age of 35 years or those suffering from recurrent pregnancy loss due to chromosomal aberrations, IVF with embryo genetic testing can be used to screen the embryo for aneuploidies in the hope of improving the implantation and lowering the SAB rates. Currently, NGS is the most used platform as it detects the structural, as well as the numerical chromosomal abnormalities, with a decreased incidence of mosaicism when compared to the other platforms [12]. Studies involving NGS as the screening platform showed a reduction in the incidence of BCP possibly as a result

Table 2 Risk factors and mechanisms leading to miscarriage

Risk factor	Possible mechanism
Adenomyosis	Luteal phase defect through progesterone resistance, altered uterine contractility, and endometrial peristalsis [#]
Advanced age: > 35 years old	abnormal oocyte morphology, compromised oocyte quality, increased risk of aneuploidies, and reduced endometrial receptivity
Endometrial polyps	Reduction of endometrial receptivity, disruption of implantation, and placentation
Endometriosis	Compromised immune status, chronic inflammatory status, defects in the luteal function, and defects in the predecidual endometrial changes, affecting the window of implantation [*]
Obesity	Not clear yet, suspected inter-relationship with other comorbidities
Lifestyle/smoking/air pollution	Induce oxidative stress, gamete DNA damage, alteration of uterine receptivity, vasoconstriction, and antimetabolic effects [&]
PCOS	Obesity
Thin endometrium on the day of ET	Abnormal endometrial decidualization in the post-implantation phase [α]
Uterine malformations	Reduced endometrial thickness at the time of ET, uneven intrauterine pressure, uncoordinated uterine contractions[β]
Immune factors	Error in the downregulation of the maternal immune system through NK causes impaired embryo implantation and increased activity in autoimmune disease, leading to damaged trophoblastic cells

References: [#] [67], [*] [38], [&] [68], [α][69], [β] [70]

of excluding mosaic embryos. Add to that, NGS-tested embryos showed that 62% of the euploid-transferred embryos correlated with an ongoing pregnancy and a live birth eventually [12]. In case embryo testing is not available, the physician should encourage blastocyst embryo transfer of the highest grade since day 5 embryo transfers were shown to be associated with lower BCP rates [9].

Alsbjerg et al. conducted a randomized controlled trial where they put to the test the theoretical benefit of adding GnRH agonist to the medicated FET cycle. The working hypothesis was that GnRH agonists can decrease the rates of early pregnancy loss. The results, despite being not statistically significant, did show a decrease in EPL rates. In the GnRH agonist group, the BCP rate was 12% and EPL was 21% as compared to the no-treatment group (25% and 33%, respectively) [72]. GnRH agonists were also studied in the setting of endometriosis and adenomyosis. In endometriosis patients, 3–6 months of GnRH agonist suppression might decrease the inflammatory milieu of the uterus and thus improve the endometrial receptivity, as well as decrease the rates of SAB [3, 73]. According to Bishop et al., medicated FET cycles represent the treatment of choice for endometriosis patients, as they decrease the complications related to the inflammatory status observed in endometriosis [74]. In adenomyosis patients, the treatment is much more complicated, and there is no consensus. Reports of ovarian suppression such as that observed in endometriosis cases have been suggested; however, there is no clear additional clinical value up to this point [67]. Overweight and obese patients are usually advised to lose weight prior to any fertility treatment given the known negative impact on pregnancy, as already mentioned in Section 0. Hence, losing weight through exercise with or without metformin, especially in the context of PCOS patients, was found to have a plausible effect on conception and reduced SAB rates [75]. In the case of endometrial polyps, in the setting of IVF and ET, Elias et al. had shown an increase in BCP in the presence of polyps; thus, performing hysteroscopic polypectomy might be beneficial [40]. Hysteroscopic septum resection is also being offered as part of uterine malformation treatment to decrease EPL rates. The existing data, however, is contradictory. The ASRM 2016 guidelines recommend septum resection, while the ESHRE 2017 guidelines recommend against it due to inconclusive supporting evidence [76, 77]. In a cohort study and another RCT performed by Rikken et al., the data analysis showed that hysteroscopic resection of uterine septum neither improved reproductive outcomes nor decreased EPL rates when compared to patients allocated to the expectant management group [78, 79]. The pregnancy loss rate was actually higher in the surgical intervention arm than in the expectant management group without being statistically significant (28% vs. 15%, respectively) [79].

In the case of autoimmune diseases, it is highly recommended to ensure tight control over the disease in the pre-conception phase, as well as during pregnancy to avoid undesirable adverse pregnancy outcomes [61].

Due to the heterogeneity of the definitions used to describe EPL events as well as the lack of properly designed RCT, some of the treatment approaches remain experimental. This limits the generalisability of the conclusion of data that is already published. Given that EPLs are events that cause significant emotional stress, performing well-designed RCT to cover the predisposing

factors to EPL and the possible treatment approaches is of utmost importance.

Conclusion

EPLs (chemical pregnancies, anembryonic pregnancies, and spontaneous miscarriages) are unfortunate events that still hamper successful outcomes of ART treatment cycles. The risk factors are related to gametes, embryos, chromosomal aberrations of the embryos, uterine environment, immune system, and endocrine and lifestyle-related factors; however, it can be multifactorial in many cases. The success of treatment approaches depends on the predisposing conditions to EPL some of which remain experimental in nature such as in endometriosis and adenomyosis cases. Carrying out IVF with genetic testing of the embryos prior to embryo transfer is a logical approach given the high percentage of EPL related to aneuploidy especially in advanced age group patients. Nevertheless, counseling patients remains one of the main pillars prior to any IVF treatment to set feasible patient expectations.

Abbreviations

aCGH	Array comparative genomic hybridization
ART	Assisted reproductive techniques
ASRM	American Society of Reproductive Medicine
AP	Anembryonic pregnancy
BCP	Biochemical pregnancy
BO	Blighted ovum
BMI	Body mass index
EPL	Early pregnancy loss
ET	Embryo transfer
FET	Frozen embryo transfer
GS	Gestational sac
G-CSF	Granulocyte colony-stimulating factor
hCG	Human chorionic gonadotropin
NGS	Next-generation sequencing
NK	Natural killer
SAB	Spontaneous abortion
RPL	Recurrent pregnancy loss
MHC	Major histocompatibility complex

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None.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Anastasia A. Salame, Mokhamad Zhaffal and Braulio Peramo. The first draft of the manuscript was written by Anastasia Salame and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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