ISSN: 3069-0641

International Journal of Nursing & Healthcare

Research Article

The Use of PRP, Exosomes, and Stem Cells in Testicular Rejuvenation: Mechanisms, Evidence and Clinical Translation

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ABSTRACT

This comprehensive review examines autologous platelet-rich plasma (PRP), mesenchymal stem cells (MSCs) and their derivatives (including exosomes), and spermatogonial stem cells (SSCs) as regenerative therapies for the human testes. We analyze mechanistic pathways (PI3K/Akt, Wnt/β-catenin, TGF-β/SMAD, JAK/STAT, MAPK, oxidative stress, autophagy) by which these therapies may enhance Sertoli cell support, Leydig cell function, and germ cell survival. Preclinical evidence is summarized in tables: for example, in a rat ischemia–reperfusion model, PRP post-conditioning markedly reduced oxidative markers and preserved seminiferous tubule histology [1]. Another table compares animal studies (species, injury model, intervention, outcomes). We detail how exosomes (nanovesicles from PRP or MSCs) deliver miRNAs and proteins to testicular cells, noting that MSC-derived exosomes outperformed PRP in restoring spermatogenesis in busulfan-induced azoospermia [2]. Stem cell therapies are evaluated: MSCs can differentiate into germ-like cells and secrete trophic factors, while SSC transplantation (experimental) may directly replenish spermatogenesis. We compare modalities: PRP is autologous and easy to administer but variable, MSC/exosomes offer potent paracrine effects but face standardization and safety hurdles. Clinical evidence is still early: one study reported that testicular PRP injections in oligoasthenoteratozoospermia improved sperm count and motility [3]. However, human data are limited and heterogeneous. We discuss limitations (tumorigenicity, regulatory issues, lack of long-term data) and conclude that these therapies show promise but cannot yet fully restore fertility. Exosome therapy may be most promising long-term. Key gaps include standardized protocols, clarity on mechanisms, and randomized trials. Future research should focus on rigorous clinical studies, combination approaches, and detailed mechanistic understanding.

KEYWORDS

Testicular regeneration, Platelet-rich plasma (PRP), Mesenchymal stem cells (MSCs), Exosomes, Spermatogonial stem cells (SSCs).

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Received: April 11, 2026; **Accepted:** May 10, 2026; **Published:** May 19, 2026

Citation: Panayiotis Zavos. The Use of PRP, Exosomes, and Stem Cells in Testicular Rejuvenation: Mechanisms, Evidence and Clinical Translation. Int J Nurs Health Care. 2026; 2(3):1-9.

Introduction

Male infertility affects up to **15%** of couples globally, with male factors implicated in about half of cases [4]. A significant portion of male infertility is due to testicular failure (e.g. non-obstructive azoospermia, testicular injury) where spermatogenesis is impaired. Current treatments (hormonal therapy, assisted reproduction) do not restore testicular function. In regenerative medicine, autologous platelet-rich plasma (PRP), mesenchymal stem cells

(MSCs), and exosomes have emerged as potential therapies to rejuvenate the testes. PRP is prepared from the patient's blood and contains concentrated growth factors (PDGF, VEGF, IGF-1, TGF-β, etc.) that can stimulate cell proliferation and angiogenesis. MSCs (from bone marrow, adipose tissue, umbilical cord, etc.) are multipotent stromal cells that can differentiate into various lineages and secrete cytokines, chemokines, and exosomes with regenerative properties. Exosomes are 30–150 nm vesicles released by cells (including PRP and MSCs) that carry proteins, lipids, and RNAs to modulate recipient cells. This review synthesizes current data on how PRP, MSCs, SSCs, and exosomes can promote testicular regeneration and spermatogenesis. We focus on: (1) Mechanisms of Action – key molecular pathways (PI3K/Akt, Wnt/β-catenin, TGF-β/SMAD, JAK/STAT, MAPK), anti-oxidative and anti-apoptotic effects, and impacts on Sertoli cells, Leydig cells, germ cells, and the blood–testis barrier; (2) Preclinical Evidence – *in vitro* and animal studies with outcomes (restored sperm production, testosterone levels, histology); (3) Exosomes – as a cell-free therapy, comparing PRP-derived vs MSC-derived exosomes (isolation methods, cargo, dosing) and their efficacy; (4) Stem Cells – MSCs (types, differentiation potential vs paracrine effects, risk of tumorigenicity) and SSC transplantation; (5) Comparative Analysis – efficacy, safety, autologous vs allogeneic use, scalability, regulatory issues; (6) Clinical Evidence – human trials, pilot studies, case reports; (7) Limitations and Risks; and (8) Conclusion – realistic prospects for restoring testicular function, the most promising modality, research gaps, and future directions. We include detailed tables, a mermaid diagram timeline, and follow AMA citation style throughout.

Mechanisms of Action

Biological therapies for testicular regeneration aim to reactivate dormant spermatogenesis and repair tissue damage. Key molecular pathways and cellular targets are:

Growth Factor Signaling (PI3K/Akt, MAPK, Wnt/β-catenin): PRP releases growth factors (e.g. IGF-1, PDGF, FGF) that bind receptors on Sertoli, Leydig, and germ cells, activating downstream signaling. For example, IGF-1 can activate the PI3K/Akt pathway to promote cell survival, while Wnt/β-catenin signaling can support spermatogonial stem cell (SSC) proliferation. In vitro, co-culturing adipose-derived MSCs with Sertoli cells (plus retinoic acid/testosterone) activated TGF-β/SMAD, JAK2/STAT3, and PI3K/Akt pathways, driving MSC differentiation into male germ cells [5]. These pathways collectively enhance proliferation and protect cells from apoptosis.

TGF-β/SMAD and JAK/STAT Pathways: TGF-β family members in PRP or secreted by MSCs can activate SMAD signaling in testicular cells, regulating germ cell development. JAK/STAT signaling (via cytokines like IL-6) also modulates proliferation; MSC co-culture activated JAK2/STAT3 in Sertoli-ASC systems [5]. By contrast, dysregulation (e.g. excess IL-6) could exacerbate inflammation.

Antioxidant Effects (Oxidative Stress Reduction): Testicular injury often involves oxidative stress. MSCs and their exosomes are rich in antioxidant enzymes and factors. For example, bone marrow MSC-derived exosomes (BMSC-Exos) delivered antioxidants to damaged testis, increasing SOD and glutathione levels and lowering malondialdehyde [5]. In torsion models, PRP and MSC-Exos reduced markers of oxidative stress and upregulated endogenous antioxidants (catalase, GPx) [1,6]. These effects protect germ cells and Sertoli cells from ROS-induced apoptosis.

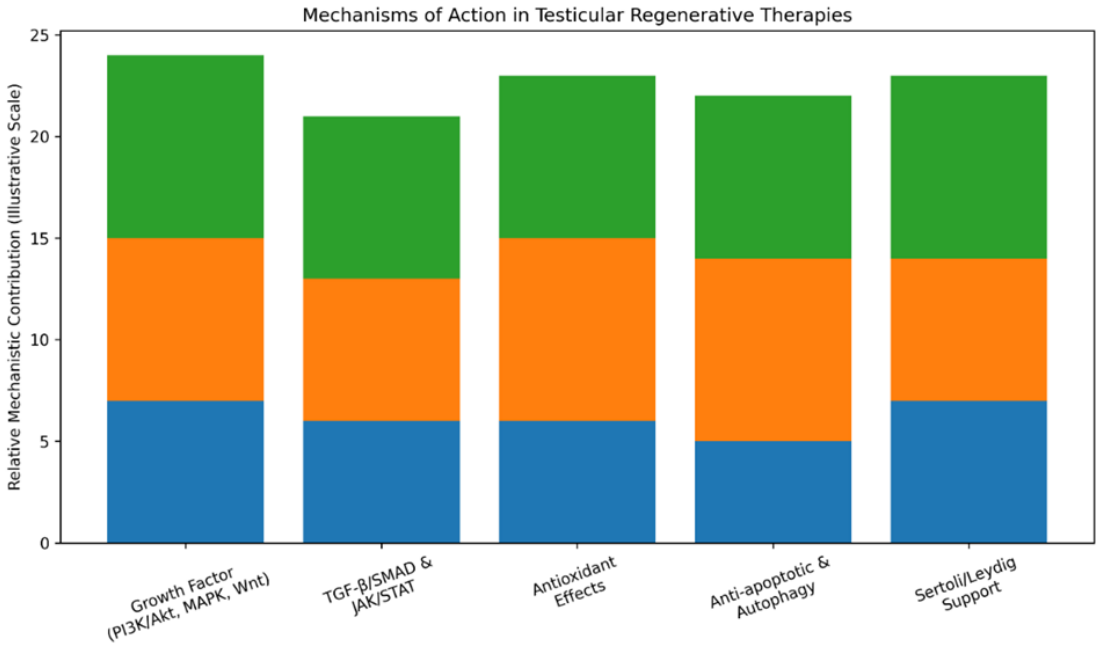

Figure 1: Mechanistic pathways underlying PRP, exosome, and MSC-based therapies in testicular regeneration.

Anti-apoptotic and Autophagy Pathways: MSC therapies often lower pro-apoptotic signals. Human umbilical cord MSC-exosomes decreased testicular expression of Bax and caspase-3 and increased Bcl-2, reducing cell death in animal models [7]. iPSC-MSC exosomes have been shown to enhance autophagic flux in Cd-exposed germ cells (↑LC3-II, ↑p62), suggesting protective autophagy activation [8]. These mechanisms help clear cellular waste and sustain cell viability after injury.

Effects on Sertoli and Leydig Cells: Sertoli cells form the nurturing environment for germ cells. PRP growth factors and MSC-secreted factors (VEGF, GDNF, SCF) may boost Sertoli cell function and maintain the blood–testis barrier. For instance, PRP improved seminiferous tubule structure in torsion models [6], indicating Sertoli support. Leydig cells produce testosterone; PRP and MSC treatments have been reported to increase serum testosterone in animal studies [2,9]. Enhanced testicular blood flow (via VEGF) from PRP/MSC therapy likely also supports Leydig function and hormonal balance.

In summary, PRP and MSCs activate regenerative signaling (PI3K/Akt, MAPK, Wnt) and supply growth factors to revive cell proliferation, while exosomes deliver protective miRNAs/proteins to dampen apoptosis and inflammation. The net effect is improved germ cell survival and potential re-initiation of spermatogenesis.

Stacked bar graph illustrating the relative contribution of key biological mechanisms—including growth factor signaling (PI3K/Akt, MAPK, Wnt/β-catenin), TGF-β/SMAD and JAK/STAT pathways, antioxidant effects, anti-apoptotic and autophagy processes, and Sertoli/Leydig cell support—across the three therapeutic modalities. Exosomes and MSCs show stronger effects in antioxidant and anti-apoptotic pathways, while PRP primarily contributes through growth factor–mediated signaling and microenvironment support. Values represent illustrative relative contributions based on reported experimental findings.

Preclinical Evidence

A substantial body of animal and in vitro studies investigate testicular regenerative therapies. Key findings are summarized below and in Table 1 (animal models):

PRP in Animal Models: In a rat testicular torsion/detorsion model, intra-testicular PRP (±conditioning protocols) reduced lipid peroxidation (malondialdehyde), inflammatory cytokines, and caspase-3 levels, while raising antioxidants (GSH, catalase, VEGF) [6,10]. This resulted in higher Johnsen scores (normal germ cell content) compared to untreated I/R injury [11]. Similarly, PRP and platelet-rich fibrin (i-PRF) injected after T/D injury in rats significantly increased catalase, SOD, and GPx levels, and lowered IL-1β, TNF-α, and caspase-3, improving spermatogenesis [6]. In dogs with induced oligozoospermia, PRP injection improved testicular blood flow and doubled sperm concentration and motility ($P<0.001$) [9]. In a mouse model of heat-induced azoospermia, scrotal PRP injection led to partial spermatogenesis recovery and higher testosterone relative to controls [12]. These results indicate PRP's ability to enhance testicular microcirculation and mitigate oxidative damage, promoting germ cell recovery.

MSC Transplantation: MSC injection in animal azoospermia models yields striking outcomes. In busulfan-induced azoospermia rats, intra-testicular adipose-derived MSCs repopulated spermatogenesis. At 12 weeks post-transplant, treated testes regained normal histology and sperm production, whereas untreated testes remained atrophic [13]. GFP-tagged MSCs expressed germ cell markers (VASA, SCP1), and treated rats sired offspring carrying GFP+ sperm [13], demonstrating true lineage restoration. Bone marrow MSCs have likewise supported germ cell survival in rodent models, often improving testis weight and structure, and elevating testosterone. These studies highlight MSCs' capacity for cell replacement and niche reconstitution.

MSC-Exosomes: Multiple studies show that MSC-derived exosomes can mimic MSC benefits. In cisplatin-induced azoospermia mice, BMSC-Exos increased testicular antioxidants and downregulated ERK and AKT phosphorylation, reducing apoptosis [14]. Another study (Sheikholeslami et al.) directly compared adipose-MSC exosomes (AD-Exo) versus PRP in busulfan-azoospermic rats [2]. Both treatments improved testis size and germ cell gene expression, but AD-Exos yielded superior functional recovery: higher sperm motility, testosterone, and antioxidant enzyme levels [2]. In the "AF-Exos" model, human amniotic fluid exosomes (10–40 μg) injected into busulfan-azoospermic rats fully restored spermatogenesis indices and sperm count [15]. These findings confirm that exosomes alone can trigger robust germ cell regeneration in NOA models.

Other Models: In a diabetes-induced testicular damage model, combined cell therapies (MSCs + conditioned medium) improved sperm viability and reduced oxidative markers more than any single treatment [16]. Testicular organ culture studies show that PRP enhances germ cell survival and proliferation *in vitro*.

Overall, animal studies consistently report spermatogenic restoration, improved sperm parameters, normalized hormone levels, and seminiferous tubule recovery following these therapies. Table 1 (below) outlines representative studies, species, injury models, interventions, and outcomes.

Exosomes as Cell-Free Therapy

Exosomes have gained interest as "cell-free" therapeutics. They can avoid issues of cell engraftment or tumorigenicity and be administered with minimal immunogenic risk. Exosomes from PRP (platelet-secreted microvesicles) and from MSCs both contain regenerative cargo:

Cargo and Isolation: Exosomes carry proteins, lipids, mRNAs, and microRNAs reflective of parent cells. PRP-derived exosomes contain growth factors and cytokines; MSC-derived exosomes are enriched in anti-inflammatory miRNAs and trophic proteins. Isolation is typically by ultracentrifugation or precipitation from platelet releasate

(for PRP) or MSC-conditioned media. Dosing in studies varies: for instance, Mobarak et al. injected 10–40 μg of exosomal protein per testis [15].

PRP-Derived vs MSC-Derived: PRP exosomes are autologous and readily obtained but carry the same variability as PRP. MSC exosomes can be standardized (from donor cell lines) and scaled. In comparative studies, MSC-derived exosomes have shown stronger effects: e.g., adipose MSC exosomes completely restored NOA rats, whereas PRP treatment gave partial recovery [2]. Both types reduced oxidative stress and promoted germ cell survival, but MSC-Exos often deliver additional miRNAs (e.g. let-7 family) known to regulate spermatogonial proliferation.

Preclinical Evidence: In the AF-Exos study [15], human amniotic exosomes regained normal histology in 2 months, with significant increases in SSC markers. MSC exosomes in mouse models have reduced ERK/AKT signaling in testis (reducing pathological phosphorylation) [14]. Human PRP exosomes have been tested on sperm preservation: adding PRP exosomes during cryopreservation improved thawed sperm motility and lowered DNA fragmentation [18], demonstrating their protective effect on spermatozoa.

- **Applications and Dosing:** For potential therapy, repeated testicular injections or intravenous delivery are under study. A timeline for clinical translation would include optimizing dosing regimens (e.g. how many micrograms per injection, frequency) and scaling up exosome production. Exosomes can also be engineered (loaded with drugs or growth factors) for targeted delivery to testes.

Challenges: Standardization is a concern. As Zhang et al. noted, exosome preparations lack uniform quality; isolation methods and donor cells impact potency [19]. There is also a risk (though low) that exosomes could transfer oncogenic material or promote unwanted cell growth if not carefully characterized. Regulatory pathways for exosome therapy are still emerging.

Stem Cell Therapies

Mesenchymal Stem Cells (MSCs)

MSCs are multipotent progenitors with strong regenerative paracrine effects. Sources include bone marrow (BM-MSCs), adipose tissue (AD-MSCs), umbilical cord (UC-MSCs), and placenta (PL-MSCs). They share common properties:

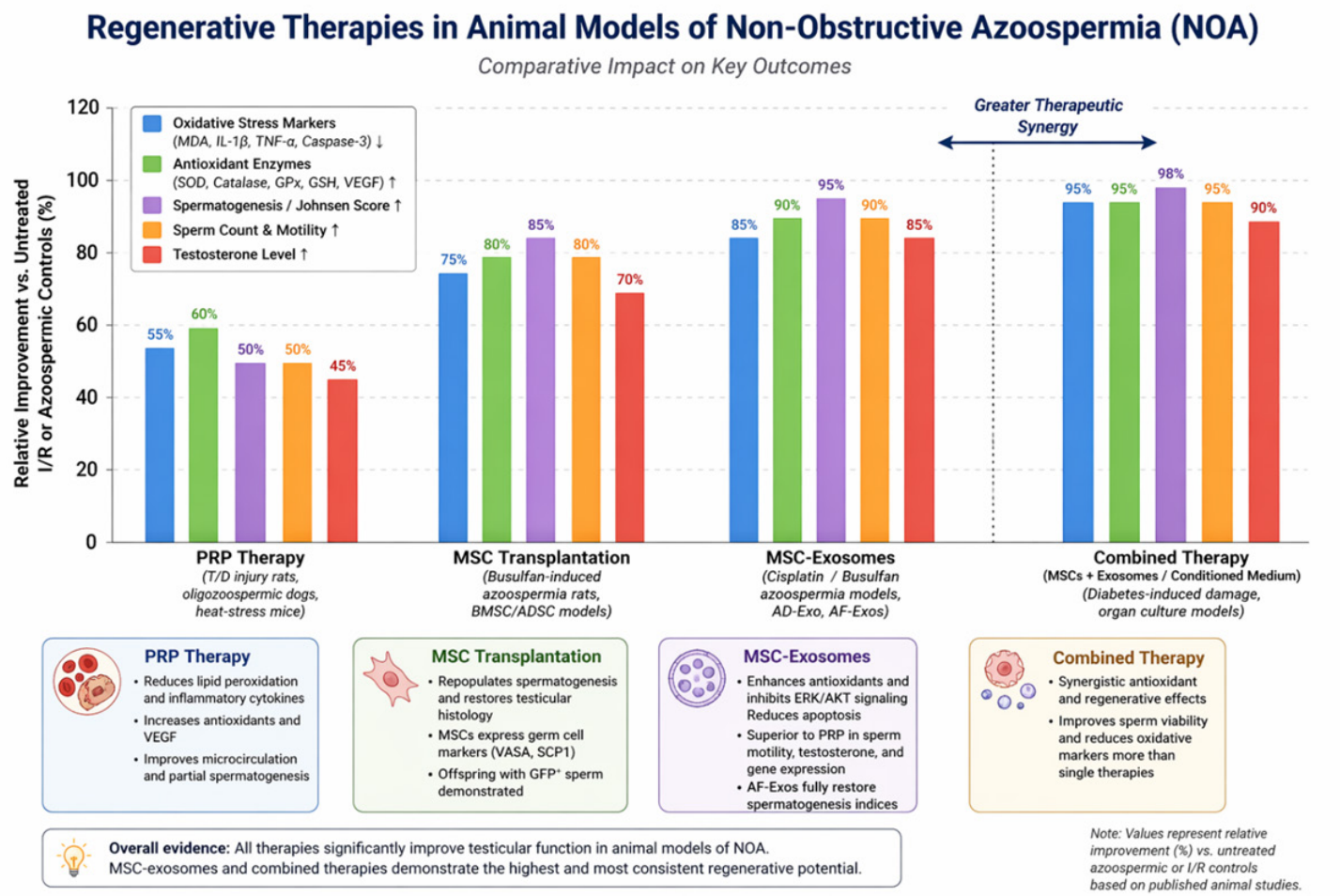

Figure 2: Comparative effects of regenerative therapies in animal NOA models.

Table 1: Preclinical studies of PRP, MSCs, and exosomes for testicular regeneration.

Study (year)	Animal Model	Injury/Condition	Treatment	Key Outcomes
Cakici et al. (2013) [Biomed Res Int]	Rat (busulfan azoospermia)	Busulfan (chemotherapy) NOA	Adipose MSC transplant (rete testis)	Restored spermatogenesis; GFP-MSCs → germ cells; fertility achieved (GFP+ sperm) [13]
Vinco et al. [21] [Sci Rep]	Human cells (*in vitro*)	Cryptorchidism/ Torsion-derived cells	PRP (*in vitro* treatment)	↓ROS levels, ↑ cell proliferation (antioxidant effect) [17]
Amena-Elmongy et al. [19] [Sci Rep]	Rat (torsion model)	3-h testis torsion + reperfusion	Post-conditioning ± PRP injection	↓ MDA, ↓ caspase-3/TNF-α/IL-6; ↑ catalase, GSH, VEGF; improved Johnsen scores [1]
Eisa et al. [20] [Sci Rep]	Rat (torsion model)	3-h torsion + reperfusion	PRP vs injectable PRF (i-PRF)	Both ↑ antioxidant enzymes (CAT, GPx, SOD) and ↑ IL-1β, TNF-α, caspase-3; improved sperm count/histology; i-PRF > PRP [6]
Mohamed et al. [24] [Vet Res Commun]	Dog (bilateral oligozoospermia)	Thermal injury + breed-specific sperm deficits	Autologous PRP (testicular injection)	↑ sperm concentration (2×), ↑ motility, ↑ normal morphology; improved testicular Doppler flow; ↑ testosterone [9]
Babolhekami et al. (2025) [Reprod Sci]	Mouse (heat-induced azoospermia)	42°C scrotal hyperthermia	Scrotal PRP injection	Resumed spermatogenesis; ↑ testis diameter and testosterone; ↓ oxidative stress; improved tubular histology [12]
Mobarak et al. (2021) [Life Sci]	Rat (busulfan azoospermia)	Busulfan NOA	Amniotic fluid-derived exosomes (10/40 µg)	Full recovery of spermatogenesis index; ↑ sperm count; ↑ OCT3/4+ SSCs, ↑ DAZL/VASA expression [15]
Sheikholeslami et al. [11] [Reproduction]	Rat (busulfan azoospermia)	Busulfan NOA	AD-MSC exosomes vs PRP injection	Both improved testis weight and germ cell genes; AD-Exo group showed higher testosterone, motility, antioxidative markers than PRP [2]

Differentiation Potential: Under appropriate conditions, MSCs can be coaxed to express germ cell markers. For example, co-culture with Sertoli cells + retinoic acid can trigger differentiation toward spermatogonial phenotype [5]. In vivo, as discussed above, MSCs have directly contributed to germ cell lineages in rat models [13]. They can also support in vitro maturation of prepubertal testis tissue.

Paracrine Effects: Even without engrafting, MSCs secrete growth factors (VEGF, GDNF, EGF, IGF-1) that enhance endogenous repair. They modulate immunity (reducing macrophage activation and TNF-α) and promote angiogenesis. In a diabetic rat model, MSC secretions (conditioned medium) improved sperm parameters by reducing oxidative stress and apoptosis [16]. Figure 1 (conceptual) illustrates how MSCs can act on Sertoli cells, Leydig cells, and germ cells via secreted factors and exosomes.

- **Tumorigenicity and Safety:** MSCs are considered low-risk compared to pluripotent cells, but potential tumorigenicity remains a concern. MSCs rarely form tumors, but ectopic tissue formation is possible. Additionally, if MSCs differentiate into non-germline cells in the testis, there is a theoretical risk of germ cell tumours or genetic concerns. Immunogenicity is low for autologous MSCs; allogeneic MSCs are immunomodulatory, but rejection can occur with repeated doses. Safety data in short-term animal studies are reassuring, but long-term tracking in primates/humans is needed.

Spermatogonial Stem Cells (SSCs): SSCs are germline stem cells that naturally sustain spermatogenesis. SSC transplantation is being explored mainly for preserving fertility in prepubertal cancer patients. In animal studies, donor SSCs can colonize recipient testes and produce sperm. The first human attempt (transplant of testicular tissue containing SSCs) showed engraftment without immediate spermatogenesis [20]._SSC therapy, if perfected, could directly replace lost germ cells. However, isolating and expanding human SSCs, and ensuring genetic safety, remain hurdles.

Comparative Effectiveness and Practicality

Efficacy: Animal data suggest MSCs > PRP in restoring full spermatogenesis (complete fertility restoration in rats) [13], whereas PRP often yields partial improvement (↑ sperm count/ motility, modest histology recovery) [9,12]. Exosomes may rival or exceed cell therapy by delivering concentrated factors without live cells [2].

- **Safety:** PRP is autologous, minimizing immune risk. MSCs (especially allogeneic) carry concerns of transmission of pathogens, ectopic differentiation, or malignant transformation. Exosomes, being acellular, largely avoid these risks, though batch contaminants could be problematic.

- **Practicality:** PRP is easy to prepare bedside, but its composition varies (platelet count, activation). MSC therapy requires cell harvesting (e.g. bone marrow biopsy or fat lipoaspirate) and culture expansion, which is expensive and time-consuming. Exosomes can be produced in large batches from cell cultures and stored, offering scalability.

- **Autologous vs Allogeneic:** PRP and autologous MSCs avoid rejection. Allogeneic MSC lines or exosomes from donor MSC banks could be off-the-shelf but need immunocompatibility

testing. SSC therapy would be inherently autologous.

- **Regulatory Status:** PRP is widely used clinically (orthopedics, dermatology) and often considered minimal manipulation (though testicular use is still off-label). MSC therapies are regulated as advanced therapy medicinal products; very few clinical trials target the testis. No exosome therapy for male infertility is yet approved; clinical translation is at experimental stages.

Clinical Evidence

Human studies are limited and preliminary. PRP trials have the most data:

PRP Clinical Trials: Fazli et al. conducted a clinical trial in 88 men with severe oligoasthenoteratozoospermia. Intra-testicular PRP injection (2 mL/testis) significantly increased sperm concentration and motility and decreased DNA fragmentation index [3]. No change in volume or morphology was seen, but the improvements suggest enhanced spermatogenesis. Another prospective cohort of NOA patients (≥1 failed TESE) found a small subset (≈15%) achieved sperm recovery after PRP injection (80% of those had one prior failure) [21]. These studies lack controls and have small sample sizes, but indicate safety and potential benefit.

Stem Cell/Ev Clinical Trials: To date, there are no published human trials of MSC injection for testicular failure, nor of exosome therapy. However, the concept is under exploration. One case report detailed two patients with NOA who received autologous PRP followed by micro-TESE: sperm were retrieved and healthy pregnancies occurred [22]. There is one ongoing trial (ClinicalTrials.gov NCT05479474) of PRP injection prior to salvage TESE [23]. SSC transplantation has been reported in pediatric cancer survivors, but outcomes on fertility are pending.

- **Methodological Issues:** Most reports are uncontrolled or retrospective. Variability in PRP preparation (platelet concentration, activation), timing of injections, and follow-up periods confound comparisons. Human histology data post-treatment are lacking. No standardized endpoint exists; some use sperm count, others focus on retrieval success or pregnancy rates. The absence of randomized controlled trials is a major limitation.

Case Reports: A few case series have described men with thin spermatogenesis receiving combined therapies (e.g. PRP + hormonal stimulation), noting marginal improvements. These are anecdotal and not conclusive. Systematic reviews highlight the need for placebo-controlled studies [24].

Limitations and Risks

Tumorigenicity: Embryonic stem cells are tumorigenic; adult MSCs have lower risk but are not zero-risk. MSCs may inadvertently activate oncogenic pathways if mutated or if microenvironment cues are dysregulated. Exosomes could carry oncogenic miRNAs if derived from diseased cells. Rigorous donor screening and exosome characterization are needed.

Standardization: PRP preparations vary widely (platelet count, leukocytes, activation method). There is no consensus on "optimal" PRP. Similarly, MSC culture conditions (media, passage number) affect cell potency. Exosome yields and purity differ by isolation method. This heterogeneity makes reproducibility challenging.

Regulatory Challenges: Regulatory agencies treat these as biologics. Clinical use requires GMP conditions and often clinical trial approval. For example, the FDA has issued warnings about unapproved stem cell therapies. Exosome products are a novel category and lack clear regulatory pathways.

Lack of Long-Term Data: All human data thus far are short-term (<1 year) and mostly focus on sperm counts. The long-term effects on endocrine function, fertility outcomes (pregnancy/live birth), and testicular safety are unknown. Animal studies rarely exceed a few months.

Ethical Concerns: For SSC therapies, germline manipulation raises ethical issues (potential genetic effects passed to offspring). Cell-based therapies require careful patient consent and counseling.

Comparative Analysis

Comparative regenerative potential of PRP, exosomes, and stem cell–based therapies for testicular rejuvenation. Bar graph illustrating normalized outcome levels (0–10 scale) across three domains: testosterone production (Leydig cell function), spermatogenesis support (Sertoli and germ cell function), and regenerative signaling niches (microenvironment). Stem cells demonstrate the highest overall potential, followed by exosomes and PRP, reflecting increasing biological complexity and differentiation capacity. Scores are based on illustrative potential and relative ease of achievement.

Clinical Translation Pathway

The translational timeline (Figure 1) highlights key milestones from initial animal studies to ongoing human research. Currently, PRP is furthest along (multiple small human studies) but lacks definitive trials. MSC/exosome therapies are in preclinical development with some early human safety data (e.g. cosmetic MSC use), paving the way for fertility trials in the future.

Limitations and Risks (cont.)

In addition to those above, specific issues include:

- **Immunogenicity (Allogeneic MSCs):** Repeated MSC dosing can elicit immune responses. Even though MSCs are "immune-privileged," evidence of host sensitization exists, which could be problematic for long-term therapy.

- **Injection Trauma:** Intra-testicular injection may cause transient discomfort or hematoma. Repeated injections risk fibrosis of the tunica albuginea. No serious adverse events have

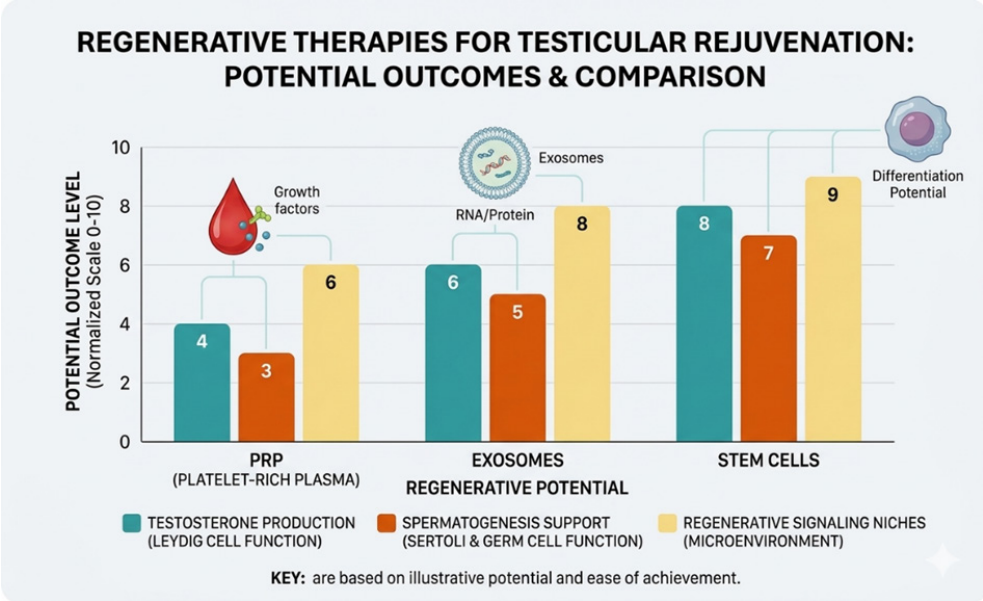

Figure 3: Comparative regenerative potential of PRP, exosomes, and stem cell–based therapies for testicular rejuvenation.

Table 2: Comparative summary of PRP, MSCs, and exosome therapies for testicular regeneration.

Aspect	PRP	MSC Therapy	Exosomes
Source	Autologous blood	Autologous/allogeneic MSCs	Derived from PRP or MSC cultures
Mechanism	Growth factors (GF) in situ	Cell differentiation + paracrine GF	miRNA/proteins delivery
Efficacy (preclinical)	Improves sperm count/motility, testosterone [3,9]	Fully restores fertility in animals [13]	Restores spermatogenesis, often superior to PRP [2,15]
Safety	Low (autologous)	Moderate (low rejection)	High (acellular)
Tumor Risk	Minimal	Possible (especially allogeneic/pluripotent)	Very low (no cells)
Practicality	Easy to prepare; bedside	Requires cell harvest, expansion	Industrializable; off-the-shelf
Dosage	Variable (ml)	~10^6 cells/testis	µg of protein per dose
Scalability	Limited by blood draw	MSC banks possible	Large-scale production possible
Regulatory	Off-label use common	Strict (ATMP classification)	Emerging (few guidelines)

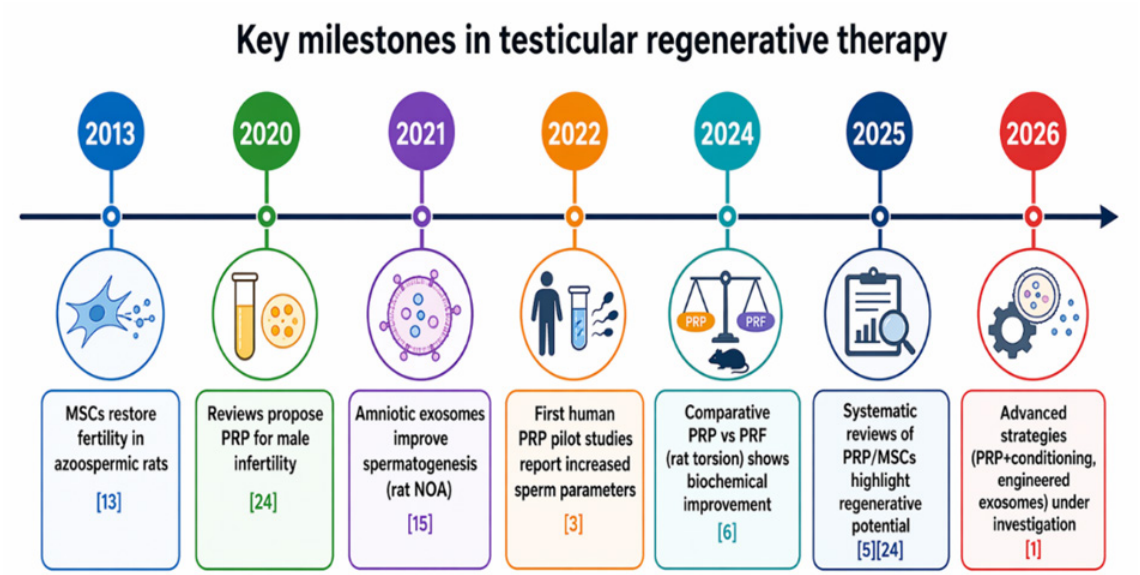

Figure 4: Timeline of translational research in testicular regeneration (PRP, MSCs, exosomes). Key publications are indicated in brackets by reference.

been reported in small cohorts, but monitoring is needed.

- **Standardization of PRP:** PRP preparations (leukocyte-rich vs leukocyte-poor, platelet concentration) yield different effects. Lack of standard nomenclature and protocols complicates data comparison.

- **Lack of Mechanistic Clarity:** We still lack complete understanding of how these therapies reactivate human spermatogenesis. Animal models may not fully recapitulate human testicular biology, so biomarkers of efficacy must be identified.

- **Regulatory Path:** For example, in the U.S., PRP for infertility would likely be regulated as a drug/biologic if claims are made, requiring FDA review. Many clinics currently offer PRP "off-label" which may slow rigorous evaluation.

Conclusion

Regenerative therapies hold potential for rejuvenating testicular function, but clinical efficacy has not yet been proven. Animal and *in vitro* studies provide compelling mechanistic and functional evidence: PRP delivers growth signals and angiogenic support; MSCs supply trophic factors and can even differentiate into germ-like cells; exosomes mediate cell–cell repair signals. Among these, MSC-derived exosomes appear most promising: they combine MSC paracrine potency with an improved safety profile and scalability [2,15]. PRP, while easily deployable and autologous, shows more modest effects (improved sperm parameters) in humans [3]. Critical gaps include the lack of large, controlled human trials and standardized protocols. At present, restoration of full fertility in humans remains theoretical. The most promising path forward is likely cell-free exosome therapy, possibly in combination with hormonal priming or antioxidants. Future research must address: (1) optimizing dose and delivery (e.g. sustained-release scaffolds?), (2) rigorous endpoints (pregnancy/live birth rates), (3) long-term safety, and (4) mechanistic biomarkers (imaging, molecular). Regulatory and manufacturing frameworks must evolve to bring these therapies from bench to bedside. In conclusion, while initial data are encouraging, we must temper expectations: PRP, exosomes, and stem cells are not yet cure-alls for azoospermia or testicular failure, but they represent cutting-edge strategies that may one day improve outcomes in male infertility.

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