Review

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How Immunotherapy Is Redefining Oncofertility in Colorectal Cancer

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Abstract

Early-onset colorectal cancer is increasing, making reproductive health an increasingly relevant survivorship issue. Immune checkpoint inhibitors have altered the management of deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) colorectal cancer, but their oncofertility implications remain insufficiently defined. We performed a focused narrative review, structured in line with the SANRA framework. PubMed/MEDLINE, international oncology and reproductive-medicine guidelines, colorectal cancer clinical practice guidelines and regulatory product information were searched up to 8 May 2026. Evidence was prioritized according to relevance to colorectal cancer treatment pathways, reproductive and sexual health, immune checkpoint inhibitor-related ovarian and endocrine effects, pregnancy and lactation safety, and fertility preservation counselling. Colorectal cancer should not be considered a single reproductive-risk scenario. Colon and rectal cancer differ anatomically, therapeutically and functionally; disease stage affects the window for fertility preservation; and dMMR/MSI-H status determines where immunotherapy is clinically relevant. Direct reproductive effects of immune checkpoint inhibitors remain uncertain and are supported mainly by biological plausibility, endocrine toxicity data, limited non-CRC ovarian-reserve data and pharmacovigilance. Conversely, indirect effects may be clinically important when immunotherapy reduces exposure to pelvic radiotherapy or radical surgery in selected dMMR/MSI-H rectal cancer patients. Counselling should be early, individualized and pathway-based.

Keywords: colorectal cancer; immunotherapy; immune checkpoint inhibitors; oncofertility; fertility preservation; ovarian reserve; reproductive health; oocyte cryopreservation; ovarian tissue cryopreservation

1. Introduction

Colorectal cancer (CRC) remains one of the most common malignancies worldwide and a major cause of cancer mortality [1]. Although traditionally regarded as a disease of later adulthood, the incidence of early-onset CRC (EOCRC), usually defined as diagnosis before 50 years of age, has

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increased in multiple populations [2,3]. Recent population-level analyses confirm that this trend is clinically relevant for women diagnosed during their reproductive years, including those in their twenties, thirties and early forties [4,5]. This epidemiologic shift matters because CRC treatment can affect reproductive health through several pathways: systemic therapy may delay attempts at conception or impair ovarian function; pelvic radiotherapy can damage ovarian and uterine function; rectal surgery can alter pelvic anatomy, autonomic innervation and sexual function; and prolonged treatment or surveillance can consume reproductive time even when ovarian reserve is not directly depleted [6–9].

In CRC, reproductive risk extends beyond a simple estimate of ovarian reserve. Rectal cancer can expose women to ovarian insufficiency, uterine radiation, dyspareunia, altered pelvic anatomy, bowel and urinary dysfunction, stoma-related body-image concerns and uncertainty about future pregnancy feasibility [7–9]. In colon cancer, reproductive counselling is generally less related to pelvic functional damage and more to systemic treatment, treatment-related delay and the timing of future pregnancy attempts [6–9]. Contemporary fertility preservation guidance recommends early counselling and referral for post-pubertal patients at risk of treatment-related infertility or reproductive compromise; however, implementation remains inconsistent when planned treatment is not classical high-risk gonadotoxic [10-12].

Immune checkpoint inhibitors (ICIs) add a distinct layer of complexity. Their established role in CRC is concentrated in tumours with deficient mismatch repair or high microsatellite instability (dMMR/MSI-H), a biologically distinct subgroup characterized by high neoantigen load and marked sensitivity to PD-1-based therapy [13]. In metastatic dMMR/MSI-H CRC, KEYNOTE-177 established pembrolizumab as a first-line standard, while CheckMate 8HW supports nivolumab plus ipilimumab as another immune-based option in unresectable or metastatic dMMR/MSI-H disease [14-17]. Contemporary guidelines for rectal and metastatic CRC now explicitly incorporate immunotherapy in selected dMMR/MSI-H settings, with treatment decisions adapted to disease stage, tumour site and molecular profile [18-22]. In non-metastatic disease, neoadjuvant and perioperative immunotherapy strategies have produced high pathological and clinical response rates in selected dMMR/MSI-H colon and rectal cancer cohorts, but their implementation remains jurisdiction-, protocol- and pathway-dependent rather than universally approved in routine practice [23-28].

The clinical question is therefore n[10–12ot whether immunotherapy should be described as reproductively neutral or gonadotoxic. In CRC, the more useful question is how immunotherapy changes the overall reproductive burden of treatment. This includes direct uncertainty regarding ovarian reserve, menstrual function, endocrine toxicity, pregnancy timing, contraception, washout and lactation, and indirect effects mediated through treatment-pathway redesign. These indirect effects are most evident in dMMR/MSI-H rectal cancer, where avoidance or deferral of pelvic radiotherapy and radical surgery may become possible for selected patients who achieve and maintain a complete clinical response. This review synthesizes the current evidence to support clinically usable, pathway-based oncofertility counselling for reproductive-age women with CRC considered for immune checkpoint blockade.

2. Materials and Methods

This focused narrative review was structured with reference to the SANRA scale for narrative reviews to improve transparency and methodological consistency [29]. PubMed/MEDLINE searches were conducted up to 8 May 2026. Search terms combined CRC and EOCRC (“colorectal cancer”, “early-onset colorectal cancer”, “young adults”, “women of reproductive age”), molecular biology (“mismatch repair deficiency”, “dMMR”, “microsatellite instability”, “MSI-H”, “Lynch syndrome”), immunotherapy (“immune checkpoint inhibitor”, “PD-1”, “PD-L1”, “CTLA-4”, “pembrolizumab”, “nivolumab”, “ipilimumab”, “dostarlimab”), and reproductive outcomes (“fertility preservation”, “oncofertility”, “ovarian reserve”, “anti-Müllerian hormone”, “AMH”, “antral follicle count”, “menstrual function”, “pregnancy”, “breastfeeding”, “hypophysitis”, “thyroiditis”, “endocrine immune-related adverse events”).

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Guideline and regulatory searches included ASCO, ESMO and ESHRE guidance, colorectal cancer clinical practice guidelines and FDA prescribing information for pembrolizumab, nivolumab, ipilimumab and dostarlimab [10–12,18–22,30–33]. CRC-specific evidence was prioritized for epidemiology, molecular stratification, treatment sequence, organ preservation and survivorship implications. Because direct CRC-specific reproductive data after ICI exposure are sparse, evidence from melanoma, mixed-tumour ICI cohorts, preclinical ovarian models, endocrine toxicity literature, pregnancy pharmacovigilance and tumour-specific oncofertility reviews was incorporated only where clinically relevant and explicitly treated as extrapolative [34–45].

No formal risk-of-bias assessment or quantitative pooling was attempted because the objective was a clinically oriented narrative synthesis rather than a systematic review. Phase II and III trials, clinical practice guidelines, regulatory labels and systematic reviews were considered high-priority evidence. Smaller cohorts, case series, pharmacovigilance reports and narrative reviews were used to capture emerging safety signals, rare reproductive scenarios or implementation issues not represented in larger datasets. Table 1 summarizes the evidence domains informing the review and lists the corresponding references used for each domain.

Table 1. Evidence sources included in the focused narrative synthesis informing this review.

Evidence type	Scope and inclusion criteria	Number of sources	References
Narrative-review methodology	SANRA framework used to structure the focused narrative review and to improve transparency and methodological consistency.	1	[29]
CRC biology, treatment pathways and immunotherapy evidence	Global CRC burden; EOCRC trends; reproductive-age women; sexual and reproductive health in EOCRC; CRC-specific fertility preservation literature; reproductive-health endpoints in cancer survivorship.	10	[1–9,46]
CRC biology, treatment pathways and immunotherapy evidence	dMMR/MSI-H biology; metastatic CRC immunotherapy trials; neoadjuvant and perioperative immunotherapy in dMMR/MSI-H colon cancer; dostarlimab and organ-preserving strategies in dMMR/MSI-H rectal cancer; CRC clinical practice guidelines and immunotherapy reviews.	24	[13–28,47–54]
Mechanistic and clinical reproductive evidence under ICI	Preclinical ovarian models; human ovarian reserve and gonadal-function data from melanoma and mixed solid-tumour cohorts; systematic and narrative reviews on ICI, fertility, pregnancy, sexual health and novel anticancer therapies; endocrine irAEs; reproductive pharmacovigilance and oncology-trial reproductive endpoints.	16	[34–45,55–58]
Fertility preservation guidance and clinical implementation	ASCO, ESMO and ESHRE fertility-preservation guidance; counselling and decisional-regret literature; ovarian reserve interpretation; oocyte/embryo cryopreservation, ovarian tissue cryopreservation.	15	[10–12,39,40,58–67]
Regulatory labels and reproductive safety information	FDA prescribing information for pembrolizumab, nivolumab, ipilimumab and dostarlimab, used for contraception interval and breastfeeding counselling.	4	[30–33]

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3. Colorectal Cancer Treatment Pathways

CRC does not represent a uniform oncofertility scenario. The reproductive implications of treatment differ between colon and rectal cancer because exposure to pelvic radiotherapy, radical pelvic surgery and multimodality treatment is largely determined by tumour site, stage and treatment strategy. In colon cancer, management is primarily defined by pathological T and N stage, resectability, emergency presentation, risk features and MMR/MSI status. In rectal cancer, management is additionally determined by pelvic MRI risk stratification, distance from the anal verge, mesorectal fascia involvement, sphincter preservation, nodal burden and the anticipated need for neoadjuvant therapy. These distinctions are clinically relevant because pelvic radiotherapy and radical rectal surgery may affect uterine capacity, ovarian reserve, pelvic autonomic function, bowel function, sexual health and pregnancy feasibility in ways that colectomy alone generally does not [7–9,18,19,21,22].

For colon cancer, stage 0 and selected low-risk T1 lesions may be managed endoscopically if resection is complete and adverse pathological features are absent; T1 lesions with high-risk features and most stage I-III cancers require oncologic colectomy with adequate lymph-node assessment. Stage I disease is generally treated with surgery alone. Stage II disease is managed after resection according to high-risk pathological features and MMR/MSI status; adjuvant fluoropyrimidine monotherapy is generally not favoured for dMMR/MSI-H stage II tumours, whereas selected high-risk pMMR/MSS patients may be considered for adjuvant chemotherapy. Stage III colon cancer usually requires postoperative oxaliplatin-based adjuvant chemotherapy, with duration and regimen adapted to recurrence risk and tolerance. In non-metastatic dMMR/MSI-H colon cancer, neoadjuvant immune checkpoint blockade has produced high pathological response rates in NICHE-2 and subsequent datasets, but this remains an emerging, jurisdiction- and pathway-dependent strategy rather than a universally approved replacement for standard surgery-based management [21,23–25].

For rectal cancer, early cT1N0 tumours with favourable histological criteria may be considered for local excision, whereas deeper or node-positive tumours are usually managed with total mesorectal excision within a risk-adapted multimodality pathway. In locally advanced rectal cancer, baseline high-resolution pelvic MRI and pretreatment MMR/MSI testing are essential because treatment may include long-course chemoradiotherapy, short-course radiotherapy, total neoadjuvant therapy, surgery, or nonoperative management after complete clinical response. For dMMR/MSI-H locally advanced rectal cancer, ASCO recommends immunotherapy as the initial approach, and ESMO guidance now includes planned dostarlimab therapy for locally advanced dMMR/MSI-H tumours, with strict response assessment and surveillance. This is the setting in which immunotherapy has the clearest indirect oncofertility relevance, because complete clinical response may allow selected patients to avoid pelvic radiotherapy and radical rectal surgery, although organ preservation must not be equated with proven reproductive safety [18,19,22,26–28].

In metastatic CRC, treatment is defined by resectability of metastases, disease tempo, prior therapies, sidedness, RAS/BRAF status, HER2 status where relevant and MMR/MSI status. For dMMR/MSI-H metastatic CRC without contraindications to immunotherapy, current evidence and contemporary ESMO guidance support first-line pembrolizumab or nivolumab plus ipilimumab as preferred immune-based options, while later-line or alternative strategies depend on prior exposure and clinical context [14–17,20]. These regimens are not fertility preservation interventions, but durable disease control can create long treatment horizons during which contraception, endocrine toxicity, treatment discontinuation, washout and future pregnancy planning become clinically relevant for selected long-term responders.

Molecular status is therefore not only a predictive biomarker for treatment selection but also a practical trigger for reproductive assessment. dMMR/MSI-H CRC is associated with increased neoantigenicity and sensitivity to checkpoint blockade [13,47]. Its prevalence varies by stage, age and tumour site, and it is generally higher in early-stage disease than in unselected metastatic CRC [47]. In young patients, dMMR/MSI-H status should also raise the possibility of Lynch syndrome, with implications for cancer surveillance, family counselling and reproductive planning, including

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possible future preimplantation genetic testing when a pathogenic familial variant is identified [48]. In reproductive-age women, confirmation of dMMR/MSI-H disease should therefore prompt not only therapeutic stratification but also timely documentation of reproductive goals and baseline reproductive vulnerability when future pregnancy is relevant.

These developments change the oncofertility landscape through two simultaneous mechanisms. First, they introduce direct reproductive uncertainty because ICIs can affect endocrine organs, require pregnancy avoidance and washout, and may plausibly perturb ovarian immune homeostasis. Second, they may indirectly reduce exposure to established reproductive harms by decreasing reliance on pelvic radiotherapy, radical rectal surgery or prolonged cytotoxic treatment in selected molecularly defined pathways. The indirect effect is most concrete in dMMR/MSI-H rectal cancer treated within organ-preservation programmes, more conditional in localized dMMR/MSI-H colon cancer, and mainly related to survivorship horizon and treatment duration in metastatic disease. Figure 1 summarizes the counselling framework discussed in this review.

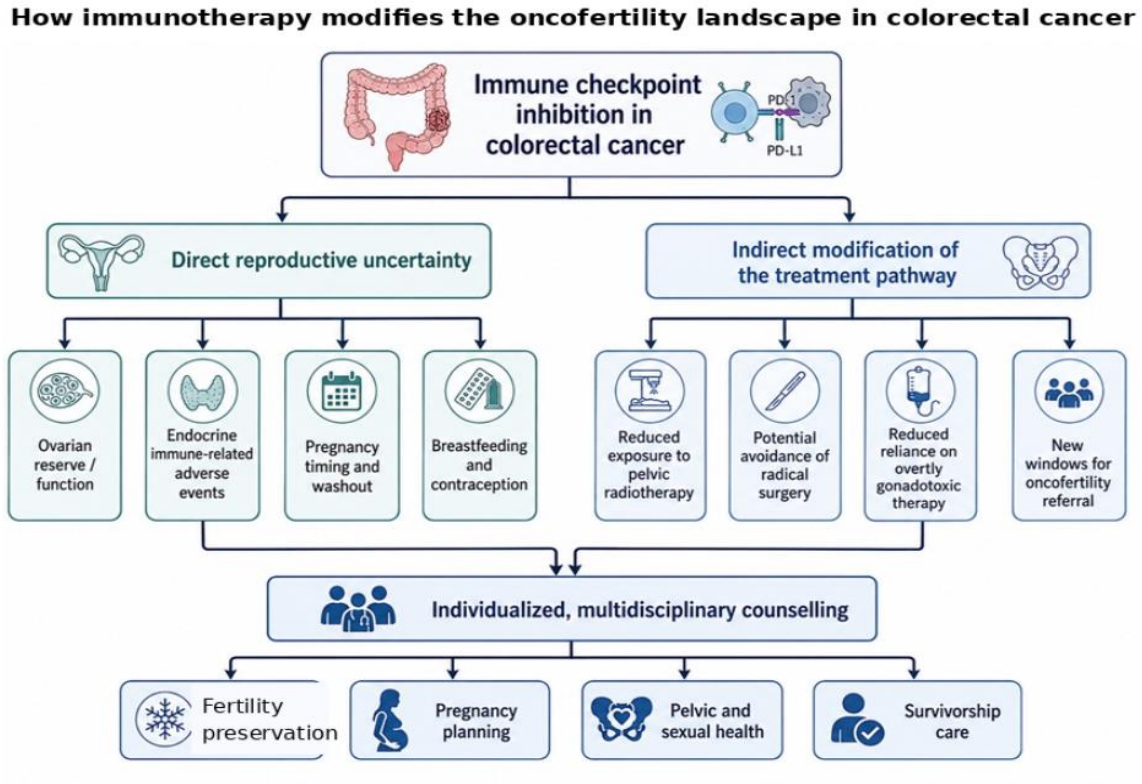

Figure 1. Conceptual framework of oncofertility in colorectal cancer treated with immune checkpoint inhibitors. Immune checkpoint inhibition may influence reproductive counselling through two complementary dimensions. Direct reproductive uncertainty includes possible effects on ovarian reserve and function, menstrual pattern, endocrine immune-related adverse events, pregnancy timing, contraception, washout and breastfeeding. Indirect pathway modification includes the possibility, in selected dMMR/MSI-H settings, of reducing exposure to pelvic radiotherapy, radical pelvic surgery or more burdensome systemic treatment. These dimensions converge into individualized multidisciplinary counselling addressing fertility preservation, pregnancy planning, pelvic and sexual health, hereditary cancer considerations and survivorship care.

4. Reproductive Biology of Checkpoint Blockade

The reproductive rationale for concern under immune checkpoint blockade differs from the logic of classical chemotherapy-induced gonadotoxicity. Alkylating agents and pelvic radiotherapy can damage the ovary through relatively direct follicular depletion, stromal injury or vascular injury. ICIs do not primarily act through these mechanisms. Their potential reproductive effects are more plausibly mediated by immune dysregulation, inflammatory signalling within the ovarian

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microenvironment, endocrine organ dysfunction and interference with maternal-fetal immune tolerance [34–40]. This distinction is clinically important: absence of classical cytotoxicity does not prove reproductive neutrality, but biological plausibility does not allow deterministic prediction of infertility.

Preclinical evidence supports concern but remains indirect. Murine models of PD-1/PD-L1 or CTLA-4 blockade have shown intra-ovarian immune activation, T-cell infiltration, cytokine signalling, follicular loss and impaired oocyte competence [34,35]. These findings suggest that checkpoint pathways may contribute to ovarian immune homeostasis and that pharmacologic blockade could alter follicular survival or oocyte quality in susceptible contexts. Translation to reproductive-age women with CRC is limited by species differences, age at exposure, dosing, tumour context, combination therapy and absence of CRC-specific prospective reproductive cohorts. Preclinical data should therefore be used to justify early counselling and structured monitoring, not to provide numerical estimates of ovarian failure.

Beyond static ovarian reserve, checkpoint disruption may also affect functional reproductive processes such as follicular growth, ovulation and luteal maintenance, because immune effector cells contribute physiologically to these events. This further supports longitudinal assessment of menstrual pattern and endocrine function alongside AMH and AFC [40].

Human data remain sparse and mostly non-CRC-specific. Systematic reviews on ICIs, fertility, pregnancy and sexual health emphasize the paucity of direct reproductive endpoints [37,38]. Similar considerations apply to other ICI-treated tumour settings, including melanoma and renal cell carcinoma, in which label-based contraception, washout and lactation requirements coexist with unresolved questions on ovarian reserve, endocrine dysfunction and post-treatment pregnancy safety [39,40]. Recent melanoma data provide mixed but clinically relevant signals: one cohort suggested generally reassuring short-term menstrual outcomes, whereas analyses of ovarian reserve markers in young women treated with ipilimumab-based therapy reported declines in anti-Mullerian hormone, although generalizability to PD-1-based CRC regimens is limited [41,42]. Taken together, current human data do not establish frequent immediate primary ovarian insufficiency after ICI exposure, but they also do not exclude subclinical ovarian reserve changes, altered stimulation response, endocrine-mediated anovulation or reproductive effects detectable only when pregnancy is attempted.

Endocrine immune-related adverse events are the most actionable reproductive mechanism. Thyroid dysfunction is common during PD-1/PD-L1 blockade, whereas hypophysitis and broader pituitary dysfunction are more characteristic of CTLA-4-containing regimens and combination strategies [43,44]. These events can impair fertility even when ovarian follicle number is preserved. Hypothyroidism can disturb ovulation and complicate pregnancy; hypophysitis can cause hypogonadotropic hypogonadism, amenorrhea, adrenal insufficiency or long-term hormone replacement needs; and fatigue, menstrual changes or sexual symptoms may be misattributed to cancer or treatment burden unless endocrine assessment is actively pursued [43,44]. In reproductive-age women treated with ICIs, endocrine follow-up is therefore not only toxicity surveillance; it is part of reproductive care.

Pregnancy requires a separate mechanistic and regulatory discussion. Maternal-fetal tolerance depends on regulated immune signalling at the decidual-placental interface, where PD-1/PD-L1 and CTLA-4 pathways contribute to limiting maternal effector responses against fetal antigens [37,45]. Blocking these pathways during pregnancy raises plausible concerns about implantation, miscarriage, placental dysfunction, fetal growth and neonatal immune effects. Human evidence remains limited and heterogeneous, with pharmacovigilance data unable to provide CRC-specific risk estimates [45]. The appropriate clinical posture is therefore conservative: pregnancy should be avoided during active ICI therapy and deferred until the relevant label-based post-treatment interval has elapsed, with individualized oncologic reassessment before conception is attempted [30–33].

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5. Fertility Preservation and Counselling

Fertility preservation counselling in CRC should be pathway-based rather than drug-label-based alone. The first step is to define tumour site, stage, molecular subtype, treatment urgency, expected local treatment burden, planned systemic therapy and the patient's reproductive goals. A 35-year-old woman with localized dMMR colon cancer considered for neoadjuvant immunotherapy has a different counselling window from a woman with dMMR/MSI-H locally advanced rectal cancer in whom organ preservation is being discussed, and both differ from a woman with metastatic disease starting urgent PD-1-based therapy. The common principle is that reproductive goals should be documented before treatment decisions become irreversible.

Pretreatment fertility counselling is clinically meaningful even when the magnitude of treatment-related reproductive risk is uncertain, because it improves preparedness, supports reproductive autonomy and can reduce subsequent decisional regret [59,60]. ASCO, ESMO and ESHRE guidance supports early counselling and timely referral to reproductive specialists for patients interested in, or uncertain about, fertility preservation [10–12]. This point is especially relevant for ICI-treated CRC: the patient may ultimately decline cryopreservation, or oncologic urgency may preclude intervention, but the decision should be informed and documented rather than omitted because immunotherapy is not a classical gonadotoxic exposure.

Baseline reproductive assessment should be explicit. It should include age, parity, desire for future pregnancy, menstrual history, prior infertility, previous ovarian or pelvic surgery, endometriosis or ovarian cysts, hormonal contraception, prior chemotherapy or radiotherapy, planned pelvic treatment, family history suggestive of hereditary cancer and the expected oncologic timeline. AMH and antral follicle count can contextualize baseline ovarian reserve and likely response to stimulation, although they do not predict spontaneous pregnancy with certainty and have not been validated as predictors of ICI-related gonadal injury [61–63]. Endometriosis and endometriomas should also be documented, because endometriotic cysts may reflect an additional baseline ovarian vulnerability and have been associated with apoptotic changes in adjacent ovarian cortex [64]. AMH and AFC have pragmatic value because they help convert an abstract risk discussion into an individualized estimate of baseline reproductive vulnerability and expected oocyte yield.

Mature oocyte cryopreservation and embryo cryopreservation remain the most established fertility preservation options for post-pubertal women when controlled ovarian stimulation can be performed without compromising oncologic care [10–12,65,66]. Modern antagonist and random-start protocols allow initiation irrespective of cycle phase and usually require approximately 10-14 days from stimulation start to oocyte retrieval [10–12]. Oocyte cryopreservation avoids the need for sperm at diagnosis and preserves autonomy for women without a partner or who do not wish to create embryos. Embryo cryopreservation may be preferred when sperm is available and embryo creation is acceptable within the applicable legal and ethical framework, and it may become particularly relevant when Lynch syndrome counselling raises future consideration of preimplantation genetic testing.

Stimulation protocols should minimize procedural risk without overstating hormone sensitivity. CRC is not generally treated as an estrogen-driven malignancy in the way some breast cancers are. The main practical questions are whether a brief stimulation interval is oncologically acceptable, whether the patient's surgical or thrombotic risk profile allows stimulation and retrieval, and whether pelvic symptoms or obstruction impose urgency. Antagonist protocols with individualized gonadotropin dosing and GnRH-agonist trigger can reduce ovarian hyperstimulation risk in high responders. Letrozole-supplemented stimulation can be considered when estradiol minimization is clinically desired, but routine use in CRC is not supported by tumour-specific evidence [10–12]. Counselling should be concrete: stimulation requires injections, ultrasound and biochemical monitoring, transvaginal oocyte retrieval and coordination with oncology to preserve the planned treatment start date.

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Ovarian tissue cryopreservation is a complementary option when stimulation is infeasible, treatment cannot be delayed or the patient wishes to maximize future reproductive and endocrine options [10–12,67]. It avoids ovarian stimulation but requires laparoscopic retrieval of ovarian cortex and later reimplantation if the tissue is to be used. In CRC, the risk of ovarian contamination is not analogous to that in haematologic malignancies, but direct or metastatic ovarian involvement must be considered in advanced disease and discussed with oncology before tissue use. In vitro maturation may be considered in highly selected time-sensitive pathways, including ovarian tissue oocyte in vitro maturation when immature oocytes are obtained during ovarian tissue cryopreservation or rescue in vitro maturation after abbreviated stimulation. Outcomes remain less consistent and less widely available than conventional mature oocyte or embryo cryopreservation, so IVM should be presented as an adjunctive yield strategy rather than a substitute for established options [10–12].

Automatic referral triggers can reduce missed counselling. Reproductive age, documented desire for future pregnancy, dMMR/MSI-H status with planned immunotherapy, anticipated pelvic radiotherapy, rectal tumour location, possible organ-preservation strategy and a clinically acceptable treatment interval should prompt referral before systemic or pelvic therapy begins. The primary objective is not to recommend cryopreservation universally, but to ensure that the decision to proceed or not proceed is informed, documented and made before the relevant therapeutic window closes. Representative clinical scenarios and related counselling priorities are summarized in Table 2.

Table 2. Representative clinical scenarios in reproductive-age women with colorectal cancer receiving or considered for immunotherapy and related counselling priorities.

Clinical scenario	Main reproductive issue	Why immunotherapy matters	Counselling priority
Localized dMMR/MSI-H colon cancer considered for neoadjuvant or perioperative immunotherapy	Need to decide whether fertility preservation can be discussed before immune-based treatment or surgery without compromising oncologic timing.	Immunotherapy may alter treatment sequence and systemic exposure, but surgery remains central in many pathways and routine use remains pathway-dependent.	Early documentation of reproductive goals; AMH/AFC and fertility history if relevant; rapid REI referral if a 10-14-day stimulation window is acceptable.
Locally advanced dMMR/MSI-H rectal cancer	High potential burden from pelvic radiotherapy, radical rectal surgery, altered pelvic anatomy, sexual dysfunction and pregnancy feasibility concerns.	PD-1 blockade may support complete clinical response and organ preservation in selected patients, potentially reducing pelvic treatment burden.	Counselling should cover fertility preservation, pelvic and sexual function, pregnancy feasibility, nonoperative management, surveillance, and contingency plans if response is incomplete.
Metastatic dMMR/MSI-H CRC treated with PD-1-based therapy, with or without CTLA-4 blockade	Long treatment horizon, uncertain conception timing, ongoing contraception, endocrine toxicity, possible treatment-free intervals after sustained disease	Immunotherapy may extend survival and, in selected durable responders, treatment interruption or surveillance may	Contraception, agent-specific washout, endocrine follow-up, ovarian reserve assessment when relevant, and individualized fertility

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	control and future pregnancy questions in durable responders.	create a treatment-free interval, but pregnancy remains unsafe during active exposure.	preservation only if oncologically feasible.
Young patient with dMMR/MSI-H CRC and suspected or confirmed Lynch syndrome	Fertility preservation may intersect with hereditary cancer counselling and possible future PGT-M.	Molecular testing affects both systemic treatment strategy and reproductive planning.	Genetics referral; discussion of oocyte versus embryo cryopreservation; clarification that PGT-M requires embryo creation and a validated familial variant-testing pathway.
Patient developing endocrine irAEs during ICI therapy	Amenorrhea, anovulation or infertility may reflect thyroiditis, hypophysitis or central hypogonadism rather than primary ovarian failure.	Endocrine toxicity is an established complication of checkpoint blockade and is more actionable than unproven direct ovarian injury.	Low threshold for thyroid and pituitary evaluation, hormone replacement when indicated, and distinction between ovarian reserve loss and endocrine-mediated reproductive dysfunction.

6. Pregnancy, Washout and Endocrine Follow-up

Contraception, washout and lactation counselling should be handled separately from the decision to cryopreserve. A woman may decline fertility preservation but still need precise pregnancy-avoidance counselling; conversely, a woman may undergo oocyte or embryo cryopreservation but still require a future transfer plan after treatment completion, drug washout and oncologic reassessment. For the ICIs most relevant to CRC, regulatory product information supports effective contraception during therapy and for a defined interval after the last dose. Typical label-based intervals are 4 months for pembrolizumab, 5 months for nivolumab, 3 months for ipilimumab and 4 months for dostarlimab [30–33]. Breastfeeding is discouraged during treatment and for the same label-specified post-treatment intervals. In combination regimens, the most conservative relevant interval should be applied, and jurisdiction-specific labels should be verified before counselling an individual patient because indications and product information may evolve. Key regulatory counselling points for currently used immune checkpoint inhibitors are summarized in Table 3.

Table 3. Label-informed reproductive safety counselling for selected immune checkpoint inhibitors relevant to colorectal cancer.

Agent	Typical CRC relevance	Post-treatment contraception interval	Breastfeeding counselling
Pembrolizumab (PD-1)	dMMR/MSI-H metastatic CRC; selected perioperative or neoadjuvant pathways depending on	Use effective contraception during treatment and for 4 months after the last dose.	Do not breastfeed during treatment and for 4 months after the last dose.

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	jurisdiction, guideline context and protocol.		
Nivolumab (PD-1)	dMMR/MSI-H metastatic CRC, including combinations with ipilimumab; selected neoadjuvant or perioperative studies.	Use effective contraception during treatment and for 5 months after the last dose.	Do not breastfeed during treatment and for 5 months after the last dose.
Ipilimumab (CTLA-4)	Combination regimens with nivolumab in metastatic or neoadjuvant dMMR/MSI-H CRC contexts.	Use effective contraception during treatment and for 3 months after the last dose.	Do not breastfeed during treatment and for 3 months after the last dose.
Dostarlimab (PD-1)	Locally advanced dMMR/MSI-H rectal cancer and selected dMMR solid tumour pathways according to regulatory status and institutional practice.	Use effective contraception during treatment and for 4 months after the last dose.	Do not breastfeed during treatment and for 4 months after the last dose.

Note: intervals summarize label-based counselling principles and should be checked against the current jurisdiction-specific product information before counselling an individual patient. In combination regimens, the longest relevant interval should generally be applied [30–33].

Localized dMMR/MSI-H colon cancer offers a defined opportunity for anticipatory counselling because diagnosis, molecular status, surgical planning and systemic treatment decisions often converge within a short interval. If neoadjuvant immunotherapy is considered, reproductive goals and fertility preservation feasibility should be assessed before treatment initiation. If upfront surgery is planned, counselling may occur postoperatively before adjuvant decisions are finalized. dMMR/MSI-H status should therefore not be used only to select systemic therapy; in reproductive-age women, it should also prompt documentation of fertility intentions and baseline ovarian reserve when future pregnancy is relevant.

In locally advanced rectal cancer, reproductive counselling should account for both gonadal and non-gonadal consequences of treatment. Traditional reproductive harm is not limited to ovarian reserve: pelvic radiotherapy may damage ovarian and uterine function, total mesorectal excision can affect autonomic nerves and sexual function, and stoma formation can influence intimacy and pregnancy planning [7–9,18,19]. In dMMR/MSI-H rectal cancer, immunotherapy introduces the possibility of organ preservation after complete clinical response, but this should not be translated into blanket reassurance. Nonoperative management requires intensive surveillance, incomplete response remains possible, and long-term obstetric, sexual and pelvic-floor outcomes after immune-based organ preservation remain incompletely characterized [26–28]. Counselling should therefore address both the potential benefit of avoiding pelvic-damaging therapy and the uncertainty that remains after favourable oncologic response.

In metastatic dMMR/MSI-H CRC, counselling is usually less about immediate cryopreservation for all patients and more about maintaining reproductive clarity during prolonged treatment. Some women require urgent therapy, making stimulation inappropriate. Others may have indolent disease, excellent response or a treatment interval in which fertility preservation could be considered. In all cases, contraception must be addressed before treatment begins. For durable responders, especially after prolonged disease control on PD-1-based therapy, including after approximately two years in regimens using fixed-duration immunotherapy, oncology teams may consider treatment interruption and surveillance in selected cases, potentially creating a treatment-free interval in which

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reproductive questions become more concrete [14,17,20]. Future pregnancy questions should still be revisited only after oncologic reassessment, confirmation of an adequate drug-free interval, endocrine stability and multidisciplinary evaluation, including maternal-fetal medicine when pregnancy is contemplated.

Longitudinal follow-up should include menstrual and endocrine assessment rather than ovarian reserve alone. Amenorrhea during or after ICI treatment may reflect pregnancy, hormonal contraception, hypothalamic suppression, weight change, stress, thyroid dysfunction, hypophysitis, primary ovarian insufficiency or treatment-related systemic illness. These diagnoses carry different implications and should not be conflated. A pragmatic follow-up strategy should document menstrual pattern, symptoms suggestive of endocrine irAEs, thyroid function, pituitary evaluation when clinically indicated and AMH/AFC when future fertility or fertility preservation remains relevant [43,44,61–63]. This is particularly important in metastatic disease, where treatment may continue for years, and in rectal cancer survivors, where pelvic and sexual function may remain central determinants of reproductive quality of life.

A pathway-based framework for oncofertility counselling in reproductive-age women with dMMR/MSI-H CRC is summarized in Figure 2.

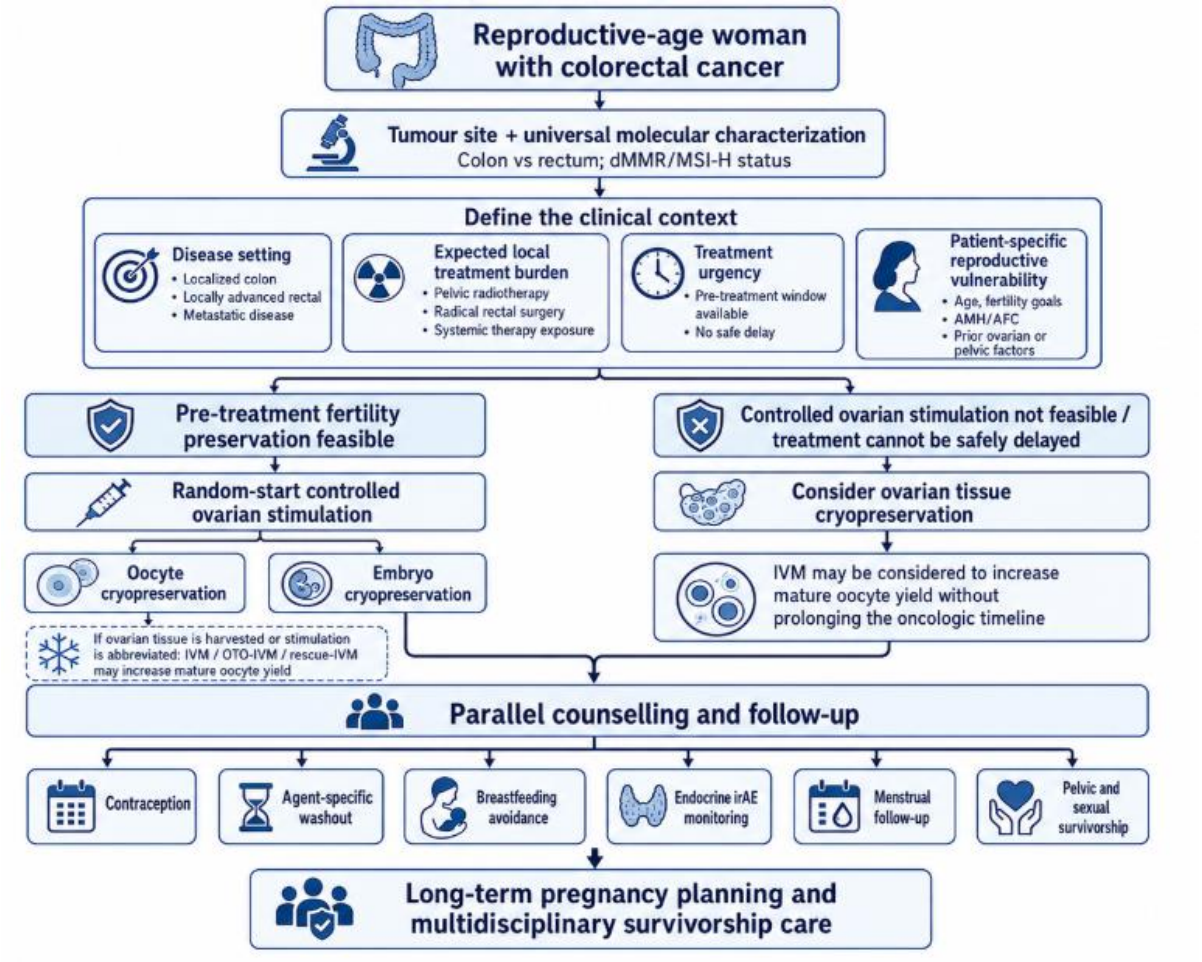

Figure 2. Proposed oncofertility pathway for reproductive-age women with dMMR/MSI-H colorectal cancer. The pathway begins with tumour-site definition and molecular characterization, because dMMR/MSI-H status identifies the subgroup in which immune checkpoint blockade may alter the oncologic pathway. Reproductive counselling should integrate disease setting, expected local treatment burden, treatment urgency and patient-specific reproductive vulnerability. Fertility preservation options should be selected according to the available oncologic window, while contraception, agent-specific washout, breastfeeding avoidance, endocrine immune-related adverse event monitoring, menstrual follow-up, pelvic and sexual survivorship, and long-term pregnancy planning should proceed in parallel rather than being deferred to survivorship.

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7. Clinical Implementation and Research Priorities

Several interpretive cautions should frame clinical implementation. First, direct CRC-specific reproductive evidence under immunotherapy is almost absent. No prospective CRC cohort currently defines how AMH, AFC, menstrual recovery, primary ovarian insufficiency, fertility preservation outcomes or post-treatment pregnancy evolve after PD-1 or CTLA-4 blockade. Counselling therefore relies on extrapolation from melanoma, mixed-tumour ICI literature, endocrine toxicity data, pregnancy pharmacovigilance and preclinical models [34–45]. This extrapolation is reasonable only if its limits are stated explicitly. Current evidence supports counselling, monitoring and prospective data collection; it does not support precise CRC-specific risk prediction.

Second, the indirect reproductive implications of immunotherapy should be neither minimized nor overstated. In dMMR/MSI-H rectal cancer, avoidance of pelvic radiotherapy or radical surgery may be highly relevant to fertility, uterine function, pelvic anatomy, sexual function and quality of life [18,19,26–28]. However, organ preservation after complete response is a monitored oncologic strategy, not a guarantee of reproductive safety. Conversely, when pelvic radiotherapy or radical surgery remains necessary, counselling should not stop at oocyte cryopreservation. It should also address uterine exposure, pelvic functional outcomes, sexual health, obstetric feasibility and the psychological effects of altered body image or stoma formation [7–9].

Third, oncology and reproductive medicine teams need shared operational language. For oncologists, fertility preservation should be described in concrete terms: who needs referral, how long stimulation usually takes, what procedures are involved, and when treatment should not be delayed. For reproductive specialists, CRC should be described by treatment pathway rather than tumour label alone: colon versus rectum, localized versus metastatic disease, dMMR/MSI-H versus pMMR/MSS biology, expected radiotherapy, surgical plan, systemic regimen and treatment duration. Miscommunication at this interface can produce two opposite errors: ICIs may be ignored because they are not considered gonadotoxic, while immune-based organ preservation may be overinterpreted as complete reproductive protection. Both forms of misclassification may compromise balanced counselling.

Experience from tumour-specific ICI oncofertility frameworks also indicates that access, reimbursement, local service capacity and absence of standardized referral triggers may determine whether counselling occurs in time, even when the clinical rationale is recognized [39,40].

Prospective CRC immunotherapy cohorts should incorporate reproductive endpoints alongside oncologic outcomes. Minimal datasets should include age, parity, fertility intentions, menstrual history, hormonal contraception, AMH, AFC, FSH/LH/estradiol when appropriate, thyroid function, pituitary toxicity, endocrine replacement, fertility preservation referral, cryopreservation uptake, oocyte yield, treatment delay, pregnancy attempts, miscarriage, live birth and obstetric outcomes. These variables should be collected at baseline, during treatment, after treatment and at defined survivorship intervals. Reproductive endpoints should also be embedded in neoadjuvant dMMR/MSI-H colon and rectal cancer platforms, where molecular selection, prospective follow-up and multidisciplinary planning already exist [23–28].

Future studies should distinguish ovarian, endocrine, uterine, pelvic, sexual and psychosocial endpoints rather than treating fertility as a single outcome. Systematic reviews of ICI-treated CRC appropriately focus on response, survival and toxicity, but reproductive endpoints remain largely absent [49–54]. Sex-specific analyses should also be expanded because immune response, toxicity, CRC biology and survivorship concerns may differ between women and men [68–71]. Recent calls to include reproductive health outcomes in standard toxicity assessment and oncology trials support this priority, and emerging mixed-tumour hormone data, pharmacovigilance analyses and broader reviews of immunotherapy and small-molecule therapy further emphasize the need for prospective, treatment-specific reproductive monitoring [46,55–58]. In reproductive-age women, the relevant question is not only whether AMH declines after ICI exposure. It is whether immunotherapy-containing pathways preserve, impair or reconfigure the conditions under which pregnancy and reproductive autonomy remain possible after CRC treatment.

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8. Conclusions

In CRC, immunotherapy primarily reshapes reproductive counselling by changing anticipated treatment exposure; its long-term reproductive safety profile remains incompletely characterized. In dMMR/MSI-H metastatic CRC, PD-1-based therapy can extend survival and make reproductive planning relevant for selected long-term responders. In localized colon cancer, neoadjuvant or perioperative immunotherapy may alter systemic treatment sequence in specialized pathways. In locally advanced dMMR/MSI-H rectal cancer, PD-1 blockade may reduce exposure to pelvic radiotherapy or radical surgery in selected complete responders, with potentially major implications for fertility, pelvic function, sexual health and future pregnancy.

At the same time, the direct reproductive effects of ICIs on ovarian reserve, menstrual function, endocrine health, pregnancy timing and long-term reproductive outcomes remain insufficiently defined. Fertility preservation counselling should therefore not be restricted to therapies already classified as highly gonadotoxic, and immunotherapy should not be presented as inherently reproductive-protective. The appropriate approach is early, individualized, pathway-based and multidisciplinary counselling that distinguishes evidence-secure recommendations from extrapolative uncertainty. Until CRC-specific reproductive data are available, high-quality care depends on timely referral, baseline reproductive assessment, realistic discussion of fertility preservation options and timelines, agent-specific contraception and washout planning, endocrine monitoring and prospective research embedded within CRC immunotherapy pathways.

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Abbreviations

AFC	Antral Follicle Count
AMH	Anti-Müllerian Hormone
ASCO	American Society of Clinical Oncology
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CRC	Colorectal Cancer
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
dMMR	Deficient Mismatch Repair
EOCRC	Early-Onset Colorectal Cancer
ESHRE	European Society of Human Reproduction and Embryology

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ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
HER2	Human Epidermal Growth Factor Receptor 2
ICI	Immune Checkpoint Inhibitor
irAE	Immune-Related Adverse Event
IVM	In Vitro Maturation
LH	Luteinizing Hormone
MEDLINE	Medical Literature Analysis and Retrieval System Online
MMR	Mismatch Repair
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability-High
MSS	Microsatellite Stable
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PGT-M	Preimplantation Genetic Testing for Monogenic Disorders
pMMR	Proficient Mismatch Repair
RAS	Rat Sarcoma Viral Oncogene Homolog
REI	Reproductive Endocrinology and Infertility
SANRA	Scale for the Assessment of Narrative Review Articles

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