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Role of Laparoscopic Ovarian Drilling in Women with Polycystic Ovarian Syndrome and Elevated Anti-Müllerian Hormone Concentrations

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Abstract:

One of the most prevalent endocrine conditions affecting women of reproductive age, polycystic ovarian syndrome (PCOS) is a leading cause of anovulatory infertility globally. Hyperandrogenism, persistent anovulation, and polycystic ovarian shape are its defining characteristics. Its pathogenesis is influenced by intricate interactions among hormonal, metabolic, and inflammatory pathways. Even with the availability of first-line ovulation induction drugs like letrozole and clomiphene citrate, a significant percentage of women continue to be resistant to medical treatment. With the benefit of restoring ovulation without raising the risk of multiple pregnancies or ovarian hyperstimulation syndrome, laparoscopic ovarian drilling (LOD) has been reintroduced as an efficient second-line treatment for clomiphene-resistant PCOS. It is believed that the operation improves follicular dynamics and restores normal endocrine function by destroying the androgen-producing ovarian stroma. Women with PCOS often have elevated levels of anti-Müllerian hormone (AMH), a sign of ovarian reserve that reflects the increased number of tiny antral follicles. Elevated AMH levels may be a predictor of treatment results and have been linked to a worse response to ovulation induction. However, there is still disagreement over the effectiveness of LOD and how it affects ovarian reserve in women with noticeably high AMH levels. With an emphasis on its potential to improve ovulation and fertility outcomes, this study attempts to assess the processes, indications, and clinical results of laparoscopic ovarian drilling in PCOS patients with elevated AMH levels.

Keywords: Polycystic ovary syndrome; Laparoscopic ovarian drilling; Anti-Müllerian hormone; Ovulation induction; Infertility.

Introduction:

It should come as no surprise that polycystic ovarian syndrome (PCOS) continues to provide difficulties for both researchers and doctors (Abu Hashim, 2015). In 1935, Stein and Leventhal reported the first successful surgical treatment of infertile women with PCOS using laparotomy and ovarian wedge excision (Abu Hashim et al., 2018).

Due to the possibility of pelvic adhesions following surgery, this practice was discontinued thirty years later, and gonadotrophins and clomiphene citrate (CC), two medications that induce ovulation, took its place (Abu Hashim et al., 2013). However, Halvard G."naess effectively revitalized surgical treatment for infertile women with PCOS in 1984 using laparoscopic ovarian drilling (LOD), which resulted in ovulation and conception rates of 92% and 80%, respectively (Abu Hashim et al., 2018). Since then, the treatment of infertile women with PCOS has relied heavily on this less painful and minimally invasive modern form of ovarian wedge excision utilizing either electrocautery (diathermy) or laser (Abu Hashim et al., 2013).

Indications For Surgery:

Since over 75% of women will ovulate with oral therapy, the American Society for Reproductive Medicine recommends laparoscopic ovarian drilling as a second-line treatment for ovulation induction in women with PCOS who do not respond to treatment with clomiphene citrate (Group, 2008). Additionally, LOD has been suggested as an adjuvant treatment prior to in vitro fertilization (IVF) cycles or as a first-line treatment for PCOS-related anovulation (Group, 2008).

Additionally, it might be the first choice for patients who find the rates of multiple gestations intolerable, women who are not trying to conceive in order to manage ovulatory and endocrine dysfunction, and those who are unable or unwilling to use conventional medical therapies (Findley & Jessup, 2020). Without an increased risk of multiple pregnancies or ovarian hyperstimulation syndrome (OHSS), LOD appears to be just as successful as gonadotrophin treatment (Group, 2008).

Mechanism of Action of LOD:

The precise mechanism of action is still mostly unclear, despite the technique's widespread use over the past 20 years. The destruction of the ovary's androgen-producing tissue, especially the theca cells in the ovarian stroma, is the most likely explanation. As a result, circulating androgen concentrations drop, which may lessen peripheral aromatization to oestrone (E1). As a result, there may be less positive feedback on LH and less negative feedback on FSH at the pituitary level, which would encourage follicular recruitment and ovulation (Li et al., 2012).

Other theories have been put forth to explain the endocrine reconstitution after LOD in addition to hormonal changes. Increased ovarian blood flow and the production of inflammatory growth factors such insulin-like growth factor-1 in reaction to heat injury may improve gonadotropin delivery and modify the ovarian-pituitary feedback loop (Ugwumadu & Kalu, 2022). Improved ovarian function may result from the removal of pro-inflammatory microenvironments within the tiny follicles, aspiration or boiling of follicular fluid due to thermal effects, and destruction of the enlarged ovarian stromal tissue (Hu et al., 2020). Additionally, alterations in the intraovarian vasculature have been linked, including a brief return to normalcy of the overexpressed levels of vascular endothelial growth factor (VEGF). LOD may assist in rebalancing the angiogenic activity that contributes to ovarian dysfunction in patients with PCOS, who frequently have elevated ovarian vascularity at baseline (Kamal et al., 2018).

Patient Selection and Predictors of Success:

20–30% of anovulatory PCOS women typically do not respond to LOD, which may be because of insufficient ovarian stroma destruction or innate ovarian resistance. Significant hyperandrogenism (testosterone ≥4.5 nmol/L or FAI ≥15), severe obesity (BMI ≥35 kg/m2), and/or prolonged infertility (>3 years) are poor prognostic factors. On the other hand, women who ovulated after LOD seemed to have a better chance of becoming pregnant if their pretreatment LH levels was high (≥10 IU/L). The results of LOD did not appear to be affected by age, the presence or absence of acne, the menstrual rhythm, the LH/FSH ratio, or ovarian volume. The clinical outcome of LOD is inversely correlated with serum levels of anti-Müllerian hormone. In PCOS women undergoing LOD, a serum AMH concentration greater than 7.7 ng/mL was found to be predictive with a bad result (Ugwumadu & Kalu, 2022).

Surgical Technique:

A monopolar diathermy needle electrode is most frequently used for LOD (Farquhar et al., 2012). Over the past thirty years, there has been a contentious debate about the lowest effective number of ovarian drills (Abu Hashim et al., 2013).

Ovulation was more common in the original LOD approach if ten or more punctures were made in both ovaries simultaneously, with each puncture having a diameter of around 3 mm and a depth of 2-4 mm, using a power setting of 200–300 W for 2-4 s. After increasing the number of drills, postoperative pelvic adhesions and ovarian failure were noted as significant drawbacks. The frequently used method of administering 640 Joules (J) per ovary (4 punctures × 4 s × 40 W) was identified by Armar et al. as the lowest effective dose with an 86% ovulation and pregnancy rate. Amer et al. later verified these results. Using four punctures to administer 600 J per ovary (4 punctures × 5s × 30W = 600 J), a 67% ovulation and pregnancy rate was observed (Abu Hashim et al., 2018).

Unilateral vs. Bilateral LOD:

The necessity of doing LOD on both ovaries as opposed to unilateral drilling has been studied by some. In a Cochrane review, Farquhar et al. (2012) examined five randomized controlled trials (RCTs) that contrasted bilateral LOD (BLOD) and unilateral LOD (ULOD). Regarding ovulation rate, pregnancy rate, live birth rate, and miscarriage rate, there were no discernible changes between unilateral and bilateral drilling. Consequently, this evidence typically supports the advice to use a ULOD rather than a BLOD.

When comparing unilateral and bilateral LOD, Abu Hashim et al. (2018) observed no difference in clinical outcomes, such as rates of ovulation, pregnancy, live birth, or miscarriage. AMH levels were found to have decreased, but they were the same for each group. The bilateral LOD group did, however, exhibit fewer antral follicles. Thus, bilateral drilling may be more dangerous for ovarian reserve but does not appear to be required for better clinical outcomes. Therefore, while seeking surgical intervention, unilateral ovarian drilling should be taken into consideration.

Ovulation and Endocrine Changes:

There is ample evidence of endocrine and ovulatory alterations following laparoscopic ovarian drilling. According to reports, 30–90% of PCOS women who undergo LOD experience regular ovulation, with a mean of 83% following monopolar diathermy (Fernandez et al., 2011). Anti-Müllerian hormone and ovarian volume are reduced by LOD, while the number of antral follicles remains same (Amer et al., 2017). The majority of research has shown that serum levels of AMH, LH, and androgen are significantly reduced following LOD, whereas FSH is either slightly elevated or mostly unaltered (Flyckt & Goldberg, 2011).

Sex hormone binding globulin is unchanged whereas androstenedione, free testosterone, and dehydroepiandrosterone sulfate are reduced. As a result, many studies have shown improvements in hirsutism and acne linked to hyperandrogenic PCOS, with the benefits frequently lasting for years. Four to nine years after laparoscopic ovarian drilling, 25% of patients with hirsutism and 40% of patients with acne showed a discernible improvement in their symptoms, according to Amer et al. Six to ten years following LOD, Mohiuddin et al. found no change in hirsutism and a reduction in acne from 38 to 14% (Findley & Jessup, 2020).

The overall impact on estradiol levels following ovarian surgery is less evident than the steady decrease in serum androgen levels. This can be attributed, in part, to variations in study size and variability, but more significantly, to the absence of reliable menstrual cycle phase-dependent monitoring. There was either no change in early and mid-follicular estradiol levels in studies where measurements coincided with cycle phase, or there was some increase in late follicular and luteal levels, the latter of which was noticeable in those who responded by resuming menstrual cyclicity. Reduced tonic LH stimulation of theca cells, which results in a lower intra-ovarian androgen burden, may be the cause of lower estradiol levels in the early proliferative phase. Consequently, there is less substrate for granulosa cell aromatase and consequently less estradiol due to the decreased thecal androgen output. Therefore, higher levels of estradiol later in the menstrual cycle probably indicate that ovarian folliculogenesis has resumed after surgery. However, progesterone levels were not significantly affected by ovarian surgery (Taylor-Giorlando & Pal, 2022).

A transient elevation in serum LH levels is commonly noted on the day after ovarian surgery, with a more consistent and sustained decline in levels thereafter. The decrease in LH levels (except for the preovulatory surge) can reportedly persist for several years following ovarian surgery. The decline in LH levels following ovarian surgery is attributable to decreased LH pulse amplitude; LH pulse frequency reportedly remains unchanged. The magnitude of decline in circulating LH was noted to be greater in those achieving spontaneous ovulation and/or conception following ovarian surgery compared to the nonresponders (Taylor-Giorlando & Pal, 2022).

Similar to LH, FSH levels also increased in most studies in the immediate postoperative phase and then declined over time to pretreatment values. Pituitary FSH secretion is driven by hypothalamic GnRH, which in turn is responsive to feedback regulation by the sex steroids. FSH is also inhibited by inhibin, which is produced by ovarian granulosa cells. Although the data on the impact of ovarian surgery on inhibin are limited, inhibin levels appear to decline in the immediate postoperative period followed by a gradual return to baseline levels within a few weeks following the procedure. Destruction of the ovarian stroma and granulosa cells can thus be hypothesized to underlie the decline in inhibin levels notable immediately following the procedure, thereby explaining the rise in endogenous FSH levels and creation of a more physiological milieu that is conducive to follicular growth (Taylor-Giorlando & Pal, 2022).

Very little research exists on the effects of LOD on lipids. In one prospective study of 34 patients, (Shokeir and El-Kannishy., 2014) reported a significant decrease in total cholesterol, low-density lipoprotein (LDL), and a significant increase in high-density lipoprotein (HDL). In another small study involving 22 patients with PCOS, Kucuk et al. did not find any significant difference in cholesterol or lipoprotein levels after LOD. Lemieux et al. also failed to find an improvement in insulin and glucose metabolism or changes to serum lipoprotein levels (Findley & Jessup, 2020).

Although chronic anovulation is a hallmark of PCOS, there are no studies examining a possible reduction in the incidence of endometrial hyperplasia or malignancy as a potential long-term benefit of the procedure (Findley & Jessup, 2020).

Complications:

The main issues that have been brought up when looking at LOD are the possibility of postoperative adhesions and decreased ovarian reserve, aside from usual difficulties that might happen during any laparoscopy. The primary causes of the eventual abandonment of bilateral ovarian wedge resection were severe adnexal adhesions and early ovarian failure resulting in reduced fertility. Even though laparoscopic ovarian drilling frequently results in postoperative adnexal adhesions, the severity and impact on fertility seem to be minimal. Between 0 to 100% of women receiving laparoscopic ovarian drilling during reoperation have been reported to suffer postoperative adhesions (Fernandez et al., 2011).

Adhesions were typically found to be minor and had no effect on pregnancy rates in trials including early second-look laparoscopy. Furthermore, the pregnancy rate after LOD is not increased by the use of adhesion barriers or early second-look laparoscopy with adhesiolysis (Findley & Jessup, 2020).

AMH and ovarian volume have been shown to decline following LOD in numerous studies. A meta-analysis of the effects of LOD on AMH and ovarian reserve was carried out by Amer et al. (2017). According to their pooled analysis, AMH was lowered by 2.13 ng/mL following LOD, and the effects persisted for up to six months.

There is no proof that this leads to decreased ovarian reserve or early ovarian failure, despite the fact that ovarian volume and AMH are markedly decreased over extended periods of time following LOD. Instead, these alterations have been seen as a normalization of the aberrant ovarian structure and function that follows the surgery (Api, 2009).

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