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Progestogens and meningioma

New evidence on levonorgestrel and desogestrel

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Meningiomas are common primary brain tumours.[1] Although most of these tumours are non-cancerous, they can cause neurological symptoms and affect quality of life. Women are more predisposed to meningiomas, with a female to male ratio of 2-3.5:1.[2-4]

Current use of progestogens has been identified as an independent risk factor for meningioma. The largest epidemiological studies studying meningioma and progestogen treatments come from the French healthcare database SNDS (Système National des Données de Santé). In the linked case-control study (doi:10.1136/bmj-2024-083981), Roland and colleagues used this database to study the relation between risk of intracranial meningioma and two additional progestogens, desogestrel and levenorgestrel.[5] An association was found with desogestrel, with low risk from short term use (odds ratio 1.02) and a slightly higher risk (odds ratio 1.70) from longer use (>5 years). No association was found between levonorgestrel and meningioma.

This study builds on previous work by the same research group studying other progestogens as potential risk factors for meningioma.[6-8] EPI-PHARE first analysed cyproterone. The study examined the incidence of meningioma (defined as neurosurgical resection, decompression, or radiotherapy for one or more intracranial meningiomas and identified using hospital codes) in girls and women aged 7-70 years using cyproterone compared with a control group that prematurely discontinued treatment and used cyproterone for a shorter duration. The study found a statistically significant increased incidence of meningioma with cyproterone and a strong dose-effect relation, with an adjusted hazard ratio of 21.7 for cumulative doses of cyproterone >60 g.[8] The same team later released data on chlormadinone (relative risk 3.1)[9] and nomegestrol (13).[10] Recently, promegestone (relative risk 2.7), medrogestone (4.1), and medroxyprogesterone (5.6) were also associated with meningioma risk.[6] All these progestogens showed a dose dependent association with meningioma.

From a practical standpoint, the risk range for desorgestrel was lower than the six previously known progestogens, and the number needed to harm was higher. Interestingly, the risk of meningioma disappeared after one year of discontinued treatment. Although direct evidence is still lacking, stopping treatment when desogestrel related meningioma is diagnosed may preclude the need for surgery as regression of meningioma can be expected in line with cessation of any other progestogen induced meningioma.[11] Notably, and contrary to sporadic meningiomas not associated with progestogens, spontaneous regression in progestogen related meningiomas can be expected in almost every patient on cessation of treatment. This phenomenon has been observed after delivery in pregnancy induced meningioma[12] or after cessation of treatment in progestogen related meningioma.[13] The pattern of tumour regression is fast, and within a few months the tumour stabilises or shrinks naturally, and symptoms improve.[13-15]

Even in France where most of the epidemiological information came from, 10% of meningiomas necessitating surgery were still due to progestogens.[6] Therefore the problem is not that progestogens are responsible for most meningiomas, but rather that some patients have had operations that could have been avoided if conservative treatment was tried first. To properly interpret the results of Roland and colleagues' study, it should be noted that the participants were treated at a time when cessation of any progestogen, even desogestrel, was not the first consideration when meningioma was diagnosed. Consequently, it is vital that a comprehensive gynaecological history is taken for every woman with meningioma. In some women with meningioma and specific gynaecological conditions, close follow-up and continued use of progestogen is acceptable after multidisciplinary consensus. For example, if a small, asymptomatic, occipital or posterior skull base meningioma is diagnosed in a patient with a severe gynaecological condition and there is no alternative option for progestogens apart from hysterectomy, close follow-up with serial magnetic resonance imaging every six months may be suggested after a meeting between gynaecologist and neurosurgeon.[16]

Currently there is no reason to modify the indications for desogestrel use, but it is important to be aware of the slightly increased risk of meningioma and that the drug should be avoided in those with a personal or family history of meningioma or breast cancer. Progestogen induced meningiomas have a propensity to locate in the anterior and middle skull base.[17] Although patients with meningiomas typically lack pathognomonic symptoms, depending on the location of the tumour they can experience clinical symptoms of headaches; focal neurological deficits, including cranial nerve deficits; seizures; mood or personality changes, confusion, or cognitive disturbances. If women present with neuro-ophthalmological symptoms, magnetic resonance imaging is required.[16]

Roland and colleagues found no excess risk of meningioma associated with levonorgestrel use. Until now it was unclear whether intrauterine devices containing levonorgestrel should be continued in patients with meningioma. As the recommendation is that any type of progestogen should be stopped on diagnosis of meningioma, affected women need to

find alternative methods of contraception. However, Roland and colleagues' study provides important information on the absence of an association between levonorgestrel and meningioma. These results are important as they open new areas for research such as the real life risk of meningioma progression in association with intrauterine devices containing levonorgestrel.

Immediate meningioma surgery or radiation without a trial period of conservative treatment is not advisable for current users of desogestrel. It is already common knowledge that stopping cyproterone, nomegestrol, chlormadinone, promegestone, medroxyprogesterone, or medrogestone precludes the need for surgery. Now we know that stopping desogestrel may also avoid unnecessary potentially harmful treatments.

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