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ORIGINAL ARTICLE

**Risk of hypospadias due to use of Pesticides among the rural families of Haryana, Uttar Pradesh and Bihar in India: An AIIMS-Delhi study highlighting the risk on agriculture produce in Pregnant Mothers & the importance of regulatory controls in the prevention of Birth Defects in Children**

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**Abstract:**

**Introduction:** The potential risk of hypospadias in children born to mothers living close to agricultural area where pesticides are used has been a topic of interest in scientific research. The present study aimed to analyze the risk of hypospadias in families living under the direct exposure to pesticide and families living under no direct exposure of pesticides.

**Material & Methods:** The present study includes 129 patients with hypospadias who underwent reconstructive surgery by a single surgeon single institution. The odds ratio (OR) of hypospadias risk has been calculated with common controls. All the patients divided in two groups one with direct exposure to pesticide i.e. farmers and other is no direct exposure i.e. profession other than farming.

**Results:** The ORs were consistently greater in group 1, indicating an increased risk of hypospadias. Patients with direct exposure to pesticides showed a significantly higher OR when compared to patients without direct exposure to pesticides and common controls.

**Conclusion:** The study found a significant association between hypospadias occurrence and pregnant mothers' with direct exposure to the pesticide. The OR was greater than 1 with highly significant p value of <0.001. The fall out of this study has serious implication on agriculture produce, particularly of interest would be designing further studies on tea plantations, vineyards & beer manufacturing units.

**Keywords:** Hypospadias, Pesticide, Agriculture, Environmental factors, Endocrine disruptors

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## **Introduction**

Hypospadias is a congenital condition where the urethral opening (meatus) is abnormally located on the ventral (underside) of the penis, rather than at the tip. It is a defect in the development of the urethra during fetal development, typically occurring between the 8th and 16th week of pregnancy. In a normal male urinary tract development, the urethral groove in the developing penis closes from the tip to the base, forming a tube that eventually becomes the urethra. In hypospadias, this closure process is disrupted, resulting in an opening that may be located anywhere along the underside of the penis, such as the head (glans), shaft, or even near the scrotum. Hypospadias is classified based on the location of the meatus, with different degrees of severity ranging from mild to severe. It is one of the most common birth defects affecting the male genitalia, occurring in approximately 1 in 200 to 300 live male births. Surgical correction is the main treatment for hypospadias, typically performed in early childhood. The aim of the surgery is to reposition the urethral opening to the tip of the penis and create a normal-looking and functional penis. The specific surgical technique used depends on the severity and location of the hypospadias. Regular follow-up care is also necessary to monitor the long-term outcomes and address any potential complications.

### ***Epidemiology of hypospadias***

The epidemiology of hypospadias has shown significant variation and remains imprecise. Incidence rates have differed across populations and time periods. According to the study conducted by Xiao Yu et al. estimated an incidence of 8 per 10,000 live male births in United States [1], while another study conducted by Bergman JE et al. an incidence of 18.6 per 10,000 births by 23 European national registries. It is worth noting that these estimates are not current and may have changed since then [2].

While a small percentage of hypospadias cases are associated with rare monogenic syndromes, the majority of cases are considered "idiopathic," meaning the cause is unknown. It is believed that a complex interplay between genetic variants and environmental factors during development may contribute to the development of hypospadias. There is evidence of a genetic predisposition, as first-degree relatives of individuals with hypospadias have a significantly increased risk of the condition (12 to 20-fold higher). Genome-wide studies have identified a few low-risk genetic variants associated with hypospadias, but the understanding of the genetic factors involved is still limited. Additionally, research into epigenetic factors, such as DNA methylation, is ongoing and may provide further insights into the development of hypospadias [3].

The contribution of environmental factors to hypospadias is presumed to be significant but has been challenging to assess. Some studies have suggested a possible link between hypospadias and decreasing male fertility, indicating the existence of a "testicular dysgenetic syndrome" in developed countries. However, further research is needed to understand the exact role of environmental factors, including exposure to agricultural pesticides and other suspected endocrine-disrupting substances [4].

### ***Use of pesticides and risk of hypospadias***

There has been scientific interest in investigating the potential association between pesticide exposure and the risk of hypospadias. Pesticides are chemicals used in agriculture, and some studies have suggested that certain pesticides may have endocrine-disrupting properties, meaning they can interfere with hormonal regulation and development [5]. Several epidemiological studies have explored the possible link between pesticide exposure and the risk of hypospadias, but the findings have

been mixed, and more research is needed to establish a clearer understanding of the relationship. Some studies have reported positive associations, while others have found no significant association or inconsistent results [6-8]. A meta-analysis published by Rocheleau CM examined the association between pesticide exposure and hypospadias risk. The analysis included 19 studies and concluded that there was a weak positive association between pesticide exposure and hypospadias risk. However, the authors noted limitations in the available data, including variations in study designs, exposure assessment methods, and potential confounding factors [9].

It's important to note that assessing the specific impact of pesticides on these conditions is challenging due to various factors, including the complexity of pesticide mixtures, differences in exposure levels, variations in study designs, and potential confounding factors. Furthermore, studies often rely on self-reported or indirect measures of pesticide exposure, which can introduce measurement errors.

#### ***The use of hazardous pesticides in agriculture***

In India, several hazardous pesticides, insecticides, and fertilizers are commonly used in agricultural practices. While the use of pesticides and insecticides is intended to protect crops from pests and diseases, improper handling or excessive use can pose risks to human health and the environment. It's important to note that specific pesticide use may vary depending on the region, crop, and farming practices. The commonly used hazardous pesticides, insecticides, and fertilizers in India are organophosphates, pyrethroids, neonicotinoids, carbamates, glyphosate, and urea.

#### ***The risk of living close to agriculture area***

The potential risk of hypospadias in children born to mothers living close to

agricultural area where pesticides are used has been a topic of interest in scientific research. Pesticides used in agriculture have raised concerns due to their potential endocrine-disrupting properties and potential adverse effects on human health. Several studies have examined the association between maternal residential proximity to agricultural areas and the risk of hypospadias in offspring. However, it's important to note that findings from these studies have been inconsistent, and more research is needed to establish a clear link [9].

To gain a comprehensive understanding of the potential risk, it is essential to consider multiple factors such as the specific types of pesticides used, application methods, timing of exposure, and individual susceptibility. Additionally, regulations, pesticide management practices, and safety precautions in agricultural areas can vary across regions and countries, affecting the potential risk.

#### **Methodology**

The present study includes patients with hypospadias who underwent reconstructive surgery by a single surgeon (MB) at Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi (India). The clinically significant cases that required surgical intervention were included in the study, while minimal glandular hypospadias cases that did not undergo surgery were excluded. The demographic data collection was conducted at Wednesday Paediatric Urology Clinic (WPUC), All India Institute of Medical Sciences, New Delhi (India) at the time of registration.

#### ***Inclusion and exclusion criteria***

The study excluded cases resulting from genetic disorders of sex differentiation or hypogonadotropic hypogonadism. The children included in the study had undergone careful examination by pediatric surgeon.

A total of 129 hypospadias cases were included from three Indian states, Bihar, Haryana and Uttar Pradesh forms the study group. The patient's characteristics have been shown in Table 1. The study aimed to analyze the risk of hypospadias in families living under the direct exposure to pesticide and families living under no direct exposure of pesticides.

### Statistical analysis

The statistical analysis has been performed to assess the risk of hypospadias in relation to families with direct exposure to pesticides and families without direct exposure. We compared incidence and severity of hypospadias and cryptorchidism cases. The odds ratio (OR) of hypospadias risk has been calculated between both the groups and compared with common controls attending the WPUC.

### Results

In group 1 (direct exposure) 17 (18.5%) patients belongs to anterior site of hypospadias in which 6 (35.3%) are sub-coronal and 11 (64.7%) were glandular, the midline site were in 31 (33.7%) patients in which 10 (32.3%) were

distal penile, 16 (51.6%) were proximal penile and 5 (16.1%) were mid-shaft. The posterior site belongs to 43 (46.7%) patients in which 18 (41.9%) were scrotal, 13 (30.2%) were peno-scrotal and 12 (27.9%) were perineal. On the other hand, in group 2 (without direct exposure) 3 (8.1%) were anterior and all were glandular, 21 (56.8%) were midline in which 6 (28.6%) were distal penile, 10 (47.6%) were proximal penile and 5 (23.8%) were mid-shaft. Posterior site belongs to 13 (35.1%) patients in which 4 (30.8%) were scrotal, 4 (30.8%) were peno-scrotal and 5 (35.5%) were perineal. Both groups, with and without direct exposure of pesticide were examined, and odds ratios (OR) were calculated. The ORs were consistently greater than 1 in group 1, indicating an increased risk of hypospadias. Patients with direct exposure to pesticides showed a significantly higher odds ratio when compared to patients without direct exposure to pesticides (Table 2).

Our findings suggest an increased risk of hypospadias associated with direct exposure to pesticide. The odds ratios were consistently higher in this group, indicating a potential association between direct exposure and hypospadias risk.

Table 1. General characteristics of the study population

S. No.	Characteristics	Numbers (%) / Mean±SD (Range)
1.	Total number of patients	n=129 (100%)
2.	Mean age (at presentation)	34.4±18.2 (12–72 months)
3.	Site of hypospadias (n=129)	
	1. Anterior	20 (15.5%)
	a) Sub-coronal	6 (30%)
	b) Glandular	14 (70%)
	2. Midline	53 (41.1%)
	a) Distal penile	17 (32.1%)
	b) Proximal penile	26 (49.1%)
	c) Midshaft	10 (18.8%)
	3. Posterior	56 (43.4%)
	a) Scrotal	22 (39.2%)
	b) Penoscrotal	17 (30.4%)
	c) Perineal	17 (30.4%)

5.	State wise participant		
		Bihar	36 (23.5%)
		Haryana	49 (32.0%)
		Uttar Pradesh	68 (44.5%)

Table 2. Odds ratios, with 95% confidence interval, of the risk of hypospadias by groups.

	Anterior site	Midline	Posterior	Controls
<b>Odds ratio</b>	32.1	2.2	10.9	1.1
<b>95% confidence interval</b>	5.66, 82.2	1.08, 4.8	4.55, 26.3	0.49, 2.39
<b>z statistic</b>	3.917	1.949	5.345	0.202
<b>p value</b>	<0.001	0.051	<0.001	0.839

## Discussion

The present study acknowledges that the observed increased prevalence of hypospadias to the rural families with direct exposure of pesticide is an indirect indication supporting the possibility of a harmful effect of pesticides. However, the study did not specifically quantify or qualify the types and quantities of pesticides used in the agriculture land due lack of awareness about the pesticides. The complexity, variety, and dynamic nature of chemicals used in agriculture land, including pesticides (such as fungicides, insecticides, herbicides, bactericides, rodenticides, and fumigants), fertilizers, and other toxic chemicals, make it challenging to precisely assess their impact.

Additionally, during the study period, there was no available database to accurately quantify the nature and load of the chemicals used by the families. Therefore, the association between direct exposure to pesticide and hypospadias risk could be influenced by various environmental factors present in the vicinity of the agriculture land, and not solely pesticides. The study recognizes that agriculture land are a prominent location for pesticide spraying and play a significant role in Indian agriculture. A limitation of the study is that it did not gather occupational data for the mothers of the cases. It is plausible to expect that a higher percentage of mothers in group 1 may be occupationally involved in crop, fruits and vegetable production

activities, potentially increasing their exposure to pesticides,

### *Evidence from Vineyard Study*

A study published by Bougnères et al. explored a significant statistical link between the occurrence of hypospadias and the residence of pregnant mothers close to vineyards, it suggests a potential association between vineyard proximity and the development of hypospadias. The study also highlighted the need for future research to account for the changing nature and loads of pesticides in modern viticulture. This indicates that pesticides used in vineyards may be a potential environmental factor contributing to the observed association. Additionally, the study suggests that identifying precise hormone-disrupting chemicals would require a deep, systematic, and specific chemical investigation of vineyards and their immediate surroundings. This type of investigation would help in understanding the potential mechanisms by which vineyard-related factors could influence the development of hypospadias [11].

### *Use of Pesticides in Tea Farming*

Pesticides used in tea farming can pose health hazards if not properly managed or used in accordance with safety guidelines. While pesticides are employed to protect tea crops from pests, diseases, and weeds, their misuse or overuse can lead to negative effects on human health and the environment such as acute

toxicity, chronic health effects, residue contamination and environmental impact. To mitigate these hazards, it is crucial for tea farmers to follow proper pesticide application techniques, adhere to recommended dosage and safety guidelines, and employ integrated pest management practices. Integrated pest management focuses on minimizing pesticide use by implementing a combination of preventive measures, biological controls, and targeted pesticide application when necessary [12-15].

### ***Use of Pesticides in Beer Brewing***

In beer production, pesticides can potentially pose health hazards if not used and managed properly throughout the brewing process. While beer itself does not typically contain high levels of pesticide residues, the ingredients used in brewing, such as barley, hops, and other adjuncts, may be treated with pesticides during cultivation can pose health hazards by agricultural use of pesticides like barley and hops, pesticide residue transfer etc. It's important to note that the overall risk of pesticide exposure through beer consumption is considered low. However, individuals with specific concerns or health conditions may choose to seek out information about the specific brewing practices and ingredient sourcing of the beers they consume [16, 17].

### ***Further evidences from the previous work done by Author***

In our previous study, we have establish polymorphisms in genes involved in xenobiotic metabolism, such as CYP1A1, GSTM1, and GSTT1, in relation to the etiology of hypospadias and their potential interaction with organochlorine pesticides. Organochlorine pesticides are a class of persistent environmental pollutants that have been implicated in various health effects, including endocrine disruption. They have been suggested as potential risk

factors for hypospadias due to their ability to interfere with hormone signaling and disrupt normal development of the male reproductive system. In another study conducted by author (MB) [18]. In another study conducted by the author explored the polymorphisms in the P450 c17 gene, specifically the 17-Hydroxylase/17,20-Lyase enzyme, in relation to estradiol and testosterone concentrations in individuals with hypospadias. The P450 c17 enzyme is involved in the synthesis of sex hormones, including estradiol and testosterone. We have established that the hormone concentrations are influenced by various factors, including genetic, environmental, and developmental factors, in addition to P450 c17 gene polymorphisms. The interplay between genetic factors, hormone metabolism, and hypospadias is complex and still not fully understood [19].

A case-control study has been conducted by the author (MB) investigating the association between polymorphisms in the SRD5A2 and CYP17 genes and hypospadias risk among Indian children provided valuable insights into the genetic factors involved in hypospadias development. The SRD5A2 gene encodes the enzyme 5 $\alpha$ -reductase type 2, which is responsible for the conversion of testosterone into its more potent form, dihydrotestosterone (DHT). Mutations or polymorphisms in the SRD5A2 gene can affect the activity or stability of the enzyme, leading to altered DHT levels. It is important to note that the relationship between SRD5A2 and CYP17 gene polymorphisms and hypospadias risk may vary among different populations. Genetic and environmental factors, as well as the interplay between multiple genes, may contribute to the development of hypospadias [20].

### ***The Anupam Verma Committee***

The government of India constituted the Anupam Verma Committee in 2013 to review 66

insecticides that were banned or restricted in other countries but still registered for domestic use in India. The committee's objective was to assess the safety and efficacy of these insecticides and make recommendations based on their findings. The committee recommended the ban on 27 pesticides as mentioned in the report. The reasons for the ban varied, but one of the key factors was the non-submission of required data for these pesticides. Without the necessary data, it becomes challenging to evaluate the safety and potential risks associated with their use. In 2016, the Anupam Verma Committee made a similar move and recommended a ban on 18 additional pesticides. These recommendations were implemented, and the ban came into effect from 2018. The committee's recommendations and subsequent bans aim to ensure the use of pesticides that have been thoroughly evaluated for their safety and efficacy, protecting human health and the environment in India [21].

The proposed ban on 27 pesticides by the Anupam Verma Committee has faced opposition from the Pesticides Manufacturers & Formulators Association of India (PMFAI). According to PMFAI, the ban would lead to a significant financial loss of up to Rs. 6000 crores. They argue that these pesticides are commonly used by farmers and are available at an affordable price, ranging from Rs. 350 to Rs. 450 per litre. In contrast, they claim that the alternatives suggested by the ban could be much more expensive, with prices ranging from Rs. 1,200 to Rs. 2,000 per litre [22].

On the other hand, environmentalists and civil society organizations have generally supported the ban on these pesticides. Their concerns focus on the potential risks associated with the use of these chemicals, including environmental pollution, human health hazards, and the adverse impacts on biodiversity and ecosystem balance. They advocate for the adoption of safer and more sustainable

alternatives to protect the environment and promote sustainable agricultural practices.

### ***Insecticides Act, 1968***

The Insecticides Act governs the use, sale, manufacture, import, export, transportation, and distribution of insecticides or pesticides in India. It provides regulations and guidelines for the safe and responsible use of these chemicals.

### ***Consumer Protection Act, 1986***

Under the Consumer Protection Act, farmers can claim compensation for losses caused by the use of insecticides or pesticides. This allows farmers to seek redress for any damages or harm resulting from the use of these chemicals.

### ***Registered Pesticides***

As of June 30, 2020, there were 273 pesticides registered for use in India, with some having restrictions on their use. These registered pesticides have undergone evaluation and approval processes to ensure their safety and efficacy. India has banned the use, manufacture, and import of certain pesticides. For example, Endosulfan, which was used in cashew plantations, is banned due to its alleged health and environmental risks. Other pesticides, such as Captafol 80% Powder and Nicotine Sulfate, are banned for domestic use but can be manufactured for export purposes. Pesticides like Monocrotophos and DDT have restrictions on their domestic use, with specific limitations or prohibitions on certain applications.

### ***Promotion of bio-pesticides***

The promotion of bio-pesticides is an important strategy to reduce the reliance on chemical pesticides and encourage sustainable agriculture practices. The central and state governments in India have taken several initiatives to promote the use of biopesticides and check the increased usage of chemical

pesticides. Both central and state governments conduct regular inspections to ensure the quality and safety of pesticides available in the market. This helps to regulate the use of chemical pesticides and maintain quality standards by organic farming schemes, farmer education, research and development etc.

The Government of India has taken several steps to promote the reduced and safe use of pesticides in agriculture. Such as integrated pest management (IPM), pesticide management, pesticide quality control, promotion of biopesticides, farmer education and training, research and development, monitoring and Surveillance etc.

These initiatives and regulatory measures aim to promote the judicious and safe use of pesticides in agriculture while minimizing their environmental and health impacts. The government continues to work towards strengthening these efforts and promoting sustainable pest management practices across the country.

## Conclusion

It's important to note that specific pesticide products may have different toxicity profiles, and the classification can vary depending on the regulatory authority and the specific assessment criteria used. It's always recommended to follow the instructions and safety precautions provided by manufacturers and regulatory agencies when handling and using pesticides.

In conclusion, our study found a significant association between hypospadias occurrence in the offsprings and pregnant mothers, with direct exposure to the pesticide (OR consistently greater than 1 with p value <0.050). However, it is important to consider a more comprehensive perspective that incorporates null findings and study limitations, particularly in the context of commonly consumed agriculture produce, including Vineyards in the regions of Maharashtra & Kerala. Future environmental research should account for the evolving nature and loads of pesticides in agriculture.

## Conflicts of interest

The author declares that they do not have conflict of interest.

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